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Signed Stephen Hurdle

Dated 4 March 2003

Patents Form 1/77

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The Patent Office

1/77

PATENT OFFICE K
28 MAR 2002
LONDON

30MAR02 E707555-1 C69803
P01/7700 0.00-0207434.2

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — AWGP//PG4784

2. Patent application number (The Patent Office will fill in this part) — 0207434.2

28 MAR 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

4735870003

United Kingdom

4. Title of the invention — Novel Compounds

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Patents ADP number *(if you know it)*

Corporate Intellectual Property

GlaxoSmithKline
Corporate Intellectual Property CN925.1
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

7960982003

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is named as an applicant, or
c) any named applicant is a corporate body
See note (d)

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	55
Claim(s)	7
Abstract	1
Drawings	

10. If you are also filing any of the following, state how many against each item.

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application
Signature H B Dawson Date 28-Mar-02

12. Name and daytime telephone number of person to contact in the United Kingdom — H B Dawson 01279 644689

Warning

After an application for a Patent has beeen filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed tf it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission unless an application has been filed at least six weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505
b) Write your answers in capital letters using black ink or you may type them.
c) If there is not enough space for all relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
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Novel Compounds

This invention relates to novel compounds, processes for their preparation, pharmaceutical formulations containing them and their use in therapy.

Inflammation is a primary response to tissue injury or microbial invasion and is characterised by leukocyte adhesion to the endothelium, diapedesis and activation within the tissue. Leukocyte activation can result in the generation of toxic oxygen species (such as superoxide anion), and the release of granule products (such as peroxidases and proteases). Circulating leukocytes include neutrophils, eosinophils, basophils, monocytes and lymphocytes. Different forms of inflammation involve different types of infiltrating leukocytes, the particular profile being regulated by the profile of adhesion molecule, cytokine and chemotactic factor expression within the tissue.

The primary function of leukocytes is to defend the host from invading organisms, such as bacteria and parasites. Once a tissue is injured or infected, a series of events occurs which causes the local recruitment of leukocytes from the circulation into the affected tissue. Leukocyte recruitment is controlled to allow for the orderly destruction and phagocytosis of foreign or dead cells, followed by tissue repair and resolution of the inflammatory infiltrate. However in chronic inflammatory states, recruitment is often inappropriate, resolution is not adequately controlled and the inflammatory reaction causes tissue destruction.

There is increasing evidence that the bronchial inflammation which is characteristic of asthma represents a specialised form of cell-mediated immunity, in which cytokine products, such as IL-4 and IL-5 released by T-helper 2 (Th2) lymphocytes, orchestrate the accumulation and activation of granulocytes, in particular eosinophils and to a lesser extent basophils. Through the release of cytotoxic basic proteins, pro-inflammatory mediators and oxygen radicals, eosinophils generate mucosal damage and initiate mechanisms that underlie bronchial hyperreactivity. Therefore, blocking the recruitment and activation of Th2 cells and eosinophils is likely to have anti-inflammatory properties in asthma. In addition, eosinophils have been implicated in other disease types such as rhinitis, eczema, irritable bowel syndrome and parasitic infections.

Chemokines are a large family of small proteins which are involved in trafficking and recruitment of leukocytes (for review see Luster, New Eng. J. Med., 338, 436-445 (1998)). They are released by a wide variety of cells and act to attract and activate various cell types, including eosinophils, basophils, neutrophils, macrophages, T and B lymphocytes. There are two major families of chemokines, CXC- (α) and CC- (β) chemokines, classified according to the spacing of two conserved cysteine residues near to the amino terminus of the

chemokine proteins. Chemokines bind to specific cell surface receptors belonging to the family of G-protein-coupled seven transmembrane-domain proteins (for review see Luster, 1998). Activation of chemokine receptors results in, amongst other responses, an increase in intracellular calcium, changes in cell shape, increased expression of cellular adhesion molecules, degranulation and promotion of cell migration (chemotaxis).

To date a number of CC chemokine receptors have been identified and of particular importance to the current invention is the CC-chemokine receptor-3 (CCR-3), which is predominantly expressed on eosinophils, and also on basophils, mast cells and Th2 cells. Chemokines that act at CCR-3, such as RANTES, MCP-3 and MCP-4, are known to recruit and activate eosinophils. Of particular interest are eotaxin and eotaxin-2, which specifically bind to CCR-3. The localization and function of CCR-3 chemokines indicate that they play a central role in the development of allergic diseases such as asthma. Thus, CCR-3 is specifically expressed on all the major cell types involved in inflammatory allergic responses. Chemokines that act at CCR-3 are generated in response to inflammatory stimuli and act to recruit these cell types to sites of inflammation, where they cause their activation (e.g. Griffiths et al., J. Exp. Med., 179, 881-887 (1994), Lloyd et al., J. Exp. Med., 191, 265-273 (2000)). In addition, anti-CCR-3 monoclonal antibodies completely inhibit eotaxin interaction with eosinophils (Heath, H. *et al.*, J. Clin. Invest. 99 (2), 178-184 (1997)), while an antibody for the CCR-3 specific chemokine, eotaxin, reduced both bronchial hyperreactivity and lung eosinophilia in an animal model of asthma (Gonzalo et al., J. Exp. Med., 188, 157-167 (1998). Thus, many lines of evidence indicate that antagonists at the CCR-3 receptor are very likely to be of therapeutic use for the treatment of a range of inflammatory conditions.

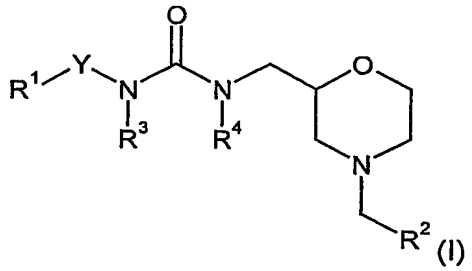
In addition to a key role in inflammatory disorders, chemokines and their receptors also play a role in infectious disease. Mammalian cytomegaloviruses, herpes viruses and pox viruses express chemokine receptor homologues, which can be activated by human CC chemokines such as RANTES and MCP-3 receptors (for review see Wells and Schwartz, Curr. Opin. Biotech., 8, 741-748, 1997). In addition, human chemokine receptors, such as CXCR-4, CCR-5 and CCR-3, can act as co-receptors for the infection of mammalian cells by microbes such as human immunodeficiency viruses (HIV). Thus, chemokine receptor antagonists, including CCR-3 antagonists, may be useful in blocking infection of CCR-3 expressing cells by HIV or in preventing the manipulation of immune cellular responses by viruses such as cytomegaloviruses.

International Patent Application publication number WO 01/24786 (Shionogi & Co. Ltd.) discloses certain aryl and heteroaryl derivatives for treating diabetes. WO 00/69830 (Torrey Pines Institute for Molecular Studies) discloses

certain diazacyclic compounds, and libraries containing them, for biological screening. WO 00/18767 (Neurogen Corporation) discloses certain piperazine derivatives as dopamine D4 receptor antagonists. United States Patent 6,031,097 and WO 99/21848 (Neurogen Corporation) discloses certain aminoisoquinoline derivatives as dopamine receptor ligands. WO 99/06384 (Recordati Industria Chimica) discloses piperazine derivatives useful for the treatment of neuromuscular dysfunction of the lower urinary tract. WO 98/56771 (Schering Aktiengesellschaft) discloses certain piperazine derivatives as anti-inflammatory agents. WO 97/47601 (Yoshitomi Pharmaceutical Industries Ltd.) discloses certain fused heterocyclic compounds as dopamine D-receptor blocking agents. WO 96/39386 (Schering Corporation) discloses certain piperidine derivatives as neurokinin antagonists. WO 96/02534 (Byk Gulden Lomberg Chemische Fabrik GmbH) discloses certain piperazine thiopyridines useful for controlling helicobacter bacteria. WO 95/32196 (Merck Sharp & Dohme Limited) discloses certain piperazine, piperidine, and tetrahydropyridine derivatives as 5-HT1D-alpha antagonists. United States Patent 5,389,635 (E.I. Du Pont de Nemours and Company) discloses certain substituted imadazoles as angiotensin-II antagonists. European Patent Application publication number 0 306 440 (Schering Aktiengesellschaft) discloses certain imidazole derivatives as cardiovascular agents.

A novel group of compounds has now been found which are CCR-3 antagonists. These compounds block the migration/chemotaxis of eosinophils and thus possess anti-inflammatory properties. These compounds are therefore of potential therapeutic benefit, especially in providing protection from eosinophil, basophil mast cell and Th2-cell-induced tissue damage in diseases where such cell types are implicated, particularly allergic diseases, including but not limited to bronchial asthma, allergic rhinitis and atopic dermatitis.

Thus, according to one aspect of the invention, there are provided compounds of formula (I):



(I)

wherein:

R^1 represents substituted or unsubstituted heteroaryl;

Y represents $-(CR_{na}R_{nb})_n-$;

R_{na} and R_{nb} are each independently hydrogen or C_{1-6}alkyl;

n is an integer from 1 to 5;

R^2 represents unsubstituted or substituted aryl or unsubstituted or substituted heteroaryl;

R^3 and R^4 each independently represent hydrogen or C_{1-6}alkyl;

and salts and solvates thereof;

with the proviso that the following compounds are excluded;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(pyridin-3-ylmethyl)urea;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[(6-methoxypyridin-3-yl)methyl]urea;

5-({[({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]-amino}methyl)nicotinamide;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(1H-indol-5-ylmethyl)urea;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(1H-indol-4-ylmethyl)urea;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[(5-methylisoxazol-3-yl)methyl]urea;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(thien-2-ylmethyl)urea;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(2-thien-2-ylethyl)urea;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-({5-[(dimethylamino)methyl]-2-furyl}methyl)urea;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[(3-methoxyisothiazol-5-yl)methyl]urea;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[(4-methyl-1,3-thiazol-2-yl)methyl]urea;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(1,3-thiazol-2-ylmethyl)urea;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[(2-methyl-1,3-thiazol-4-yl)methyl]urea;

methyl 2-({[({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]-amino}-methyl)--4-methyl-1,3-thiazole-5-carboxylate;

N-[(5-amino-1-phenyl-1H-pyrazol-4-yl)methyl]-N'-{[4-(3,4-dichlorobenzyl)--morpholin-2-yl]methyl}urea;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)urea;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-({5-[(dimethylamino)--methyl]thien-2-yl}methyl)urea;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(2-furylmethyl)urea;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[(2-methyl-2H-tetraazol-5-yl)methyl]urea;

N-{[3-(4-chlorophenyl)isoxazol-5-yl]methyl}-N'-{[(2S)-4-(3,4-dichlorobenzyl)-

-morpholin-2-yl]methyl}urea;
N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[(2-methyl-2H-tetraazol--5-yl)methyl]urea;
N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[(4-methyl-1,3-thiazol-2--yl)methyl]urea;
N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(1,3-thiazol-2-ylmethyl)--urea, and;
N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-{[3-(4-methoxyphenyl)--isoxazol-5-yl]methyl}urea.

Examples of the heteroaryl group, R^1, include thiazolyl, thiophenyl, furanyl, pyrazinyl, tetrazolyl, triazolyl, oxadiazolyl, isoxazolyl, and pyrazolyl.

When R^1 is substituted heteroaryl, suitable substituents include carboxy; $R^5R^6NC(O)$-, wherein R^5 and R^6 may each independently represent hydrogen or C_{1-6}alkyl, or R^5 and R^6 may represent a $-(CH_2)_p-$ group wherein p is an integer from 3 to 7 so that, together with the nitrogen atom to which they are attached, a 4 to 8-membered heterocyclyl ring is formed; C_{3-8}cycloalkylaminocarbonyl; amino; C_{1-6}alkylsulphonylamino; C_{1-6}alkylcarbonyl; C_{1-6}alkyl; C_{1-6}alkoxycarbonyl; unsubstituted heteroaryl; heteroaryl substituted with C_{1-6}alkyl, halo, C_{1-6}alkoxy, or hydroxy; halo; C_{1-6}alkoxy; nitro; C_{1-6}alkylsulphonyl; hydroxy; C_{1-6}alkoxyC_{1-6}alkyl; C_{1-6}alkylthio; mono- and-(di-C_{1-6}alkyl)amino; and C_{1-6}alkylcarbonylamino.

When R^1 is substituted by unsubstituted or substituted heteroaryl, examples of said heteroaryl group include isoxazolyl.

Suitably, R^1 is unsubstituted or substituted isoxazolyl, unsubstituted or substituted pyrazinyl, unsubstituted or substituted tetrazolyl, unsubstituted or substituted triazolyl, unsubstituted or substituted pyrazolyl, unsubstituted or substituted furanyl, unsubstituted or substituted thiazolyl, unsubstituted or substituted thiophenyl, or unsubstituted or substituted oxadiazolyl.

When R^1 is substituted isoxazolyl, suitable substituents include C_{1-6}alkyl, C_{1-6} alkoxycarbonyl and $R^5R^6NC(O)$- wherein R^5 and R^6 may each independently represent hydrogen or C_{1-6}alkyl.

When R^1 is substituted tetrazolyl, suitable substituents include C_{1-6}alkyl.

When R^1 is substituted triazolyl, suitable substituents include amino and C_{1-6}alkyl.

When R^1 is substituted oxadiazolyl, suitable substituents include C_{1-6}alkyl; C_{1-6}alkoxycarbonyl; $R^5R^6NC(O)$- wherein R^5 and R^6 may each independently represent hydrogen or C_{1-6}alkyl or R^5 and R^6 may represent a $-(CH_2)_p-$ group wherein p is an integer from 3 to 7 so that, together with the nitrogen atom to which they are attached, a 4 to 8-membered heterocyclyl ring is formed; C_{3-8}cycloalkylaminocarbonyl; and isoxazolyl substituted with C_{1-6}alkyl.

When R^1 is substituted pyrazolyl, suitable substituents include C_{1-6}alkyl.

When R^1 is substituted furanyl, suitable substituents include carboxy; C_{1-6} alkoxycarbonyl; $R^5R^6NC(O)$- wherein R^5 and R^6 may each independently represent hydrogen or C_{1-6}alkyl.

When R^1 is substituted thiazolyl, suitable substituents include carboxy; C_{1-6} alkoxycarbonyl; $R^5R^6NC(O)$- wherein R^5 and R^6 may each independently represent hydrogen or C_{1-6}alkyl.

When R^1 is substituted thiophenyl, suitable substituents include carboxy; C_{1-6} alkoxycarbonyl; $R^5R^6NC(O)$- wherein R^5 and R^6 may each independently represent hydrogen or C_{1-6}alkyl.

More suitably, R^1 is 2-(*iso*-propyl)tetrazol-5-yl, 1,2,3-triazol-4-yl, 1-methyl-1,2,3-triazol-4-yl, 2-methyl-1,2,3-triazol-4-yl, 1-methyl-1,2,4-triazol-3-yl, 5-methyl-1,2,4-oxadiazol-3-yl, 3-ethoxycarbonyl-1,2,4-oxadiazol-5-yl, 3-methylaminocarbonyl-1,2,4-oxadiazol-5-yl, 3-ethylaminocarbonyl-1,2,4-oxadiazol-5-yl, 5-(5-methylisoxazol-3-yl)-1,2,4-oxadiazol-3-yl, 5-methylaminocarbonyl-1,2,4-oxadiazol-3-yl, 2-methyl-1,3,4-oxadiazol-5-yl, pyrazin-2-yl, 3-methylisoxazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 3-(pyrrolidine-N-carbonyl)-1,2,4-oxadiazol-5-yl, 3-(*iso*-propylaminocarbonyl)-1,2,4-oxadiazol-5-yl, 5-(ethylaminocarbonyl)-1,2,4-oxadiazol-3-yl, 3-(cyclopropylaminocarbonyl)-1,2,4-oxadiazol-5-yl, 3-(*iso*-propyl(methyl)aminocarbonyl)-1,2,4-oxadiazol-5-yl, 1-*iso*-propyltetrazol-5-yl, tetrazol-5-yl, 2-amino-1,3,4-triazol-5-yl, 5-methylisoxazol-3-yl, 1-methylpyrazol-4-yl, 2-methylaminocarbonyl-1,3,4-oxadiazol-5-yl, 2-ethylaminocarbonyl-1,3,4-oxadiazol-5-yl, 2-(*iso*-propylaminocarbonyl)-1,3,4-oxadiazol-5-yl, 2-carboxyfuran-5-yl, 2-(ethoxycarbonyl)furan-5-yl, 2-(methylaminocarbonyl)furan-5-yl, 2-(ethylaminocarbonyl)furan-5-yl, 2-(*iso*-propylaminocarbonyl)furan-5-yl, 1-methylpyrazol-3-yl, pyrazol-3-yl, 3-methylpyrazol-5-yl, 3-(ethoxycarbonyl)isoxazol-5-yl, 2-methyltetrazol-5-yl, 3-(methylaminocarbonyl)furan-5-yl, 3-(ethylaminocarbonyl)furan-5-yl, 3-(*iso*-propylaminocarbonyl)furan-5-yl, 3-(methylaminocarbonyl)isoxazol-5-yl, 3-(ethylaminocarbonyl)isoxazol-5-yl, 3-(dimethylaminocarbonyl)isoxazol-5-yl, 3-(*iso*-propylaminocarbonyl)isoxazol-5-yl, 4-(methylaminocarbonyl)thiazol-2-yl, 4-(ethylaminocarbonyl)thiazol-2-yl, 4-(dimethylaminocarbonyl)thiazol-2-yl, 4-(*iso*-propylaminocarbonyl)thiazol-2-yl, 4-(ethoxycarbonyl)thiazol-2-yl, 4-carboxythiazol-2-yl, 2-(methylaminocarbonyl)thiophen-5-yl, 2-(ethylaminocarbonyl)thiophen-5-yl, 2-(*iso*-propylaminocarbonyl)thiophen-5-yl, 2-(methylaminocarbonyl)thiophen-4-yl, 2-(ethylaminocarbonyl)thiophen-4-yl, 2-(*iso*-propylaminocarbonyl)thiophen-4-yl, 2-(methoxycarbonyl)thiophen-4-yl, 2-

carboxythiophen-4-yl, 2-(methoxycarbonyl)thiophen-5-yl, 2-carboxythiophen-5-yl, 3-(ethoxycarbonyl)furan-5-yl, or 3-carboxyfuran-5-yl.

Suitably, R_{na} and R_{nb} are both hydrogen.

Suitably, n is 1.

Suitably, R^3 and R^4 are both hydrogen.

When R^2 is aryl, examples include phenyl.

When R^2 is substituted aryl, suitable substituents include cyano, perhaloC_{1-6}alkyl, amido, halo, C_{1-6}alkyl, C_{1-6}alkoxycarbonyl, mono- and di-(C_{1-6}alkyl)aminocarbonyl, C_{1-6}alkoxy, nitro, C_{1-6}alkylsulphonyl, hydroxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkylthio, mono- and-di-(C_{1-6}alkyl)amino, and C_{1-6}alkylcarbonylamino.

When R^2 is heteroaryl, examples include thiophenyl.

When R^2 is substituted heteroaryl, suitable substituents include cyano, perhaloC_{1-6}alkyl, amido, halo, C_{1-6}alkyl, C_{1-6}alkoxycarbonyl, mono- and di-(C_{1-6}alkyl)aminocarbonyl, C_{1-6}alkoxy, nitro, C_{1-6}alkylsulphonyl, hydroxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkylthio, mono- and-di-(C_{1-6}alkyl)amino, and C_{1-6}alkylcarbonylamino.

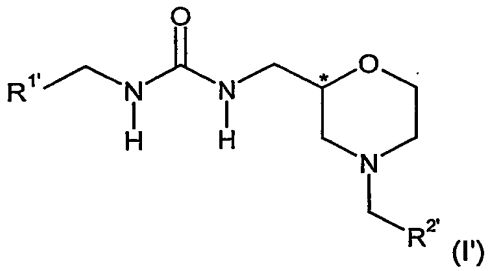
Suitably, R^2 is unsubstituted or substituted phenyl or unsubstituted or substituted thiophenyl.

When R^2 is substituted phenyl suitable substituents include halo.

More suitably, R^2 is phenyl substituted with chloro or fluoro.

Preferably, R^2 is 3-chloro-4-fluorophenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl, 3-chlorophenyl, 2-chlorothiophen-5-yl, or 4-fluorophenyl.

There exists a preferred subgroup of compounds of formula (I), being of formula (I')



(I')

wherein;

$R^{1'}$ is unsubstituted or substituted heteroaryl, and;

$R^{2'}$ is phenyl substituted by halo.

Suitably, $R^{1'}$ is unsubstituted or substituted furanyl, unsubstituted or substituted pyrazolyl, unsubstituted or substituted tetrazolyl, unsubstituted or substituted triazolyl, unsubstituted or substituted oxadiazolyl, unsubstituted or substituted pyrazinyl, unsubstituted or substituted thiazolyl, unsubstituted or substituted thiophenyl, or unsubstituted or substituted isoxazolyl.

Preferably, $R^{1'}$ is 2-(*iso*-propyl)tetrazol-5-yl, 1,2,3-triazol-4-yl, 1-methyl-1,2,3-triazol-4-yl, 2-methyl-1,2,3-triazol-4-yl, 1-methyl-1,2,4-triazol-3-yl, 5-methyl-1,2,4-oxadiazol-3-yl, 3-ethoxycarbonyl-1,2,4-oxadiazol-5-yl, 3-methylaminocarbonyl-1,2,4-oxadiazol-5-yl, 3-ethylaminocarbonyl-1,2,4-oxadiazol-5-yl, 5-(5-methylisoxazol-3-yl)-1,2,4-oxadiazol-3-yl, 5-methylaminocarbonyl-1,2,4-oxadiazol-3-yl, 2-methyl-1,3,4-oxadiazol-5-yl, pyrazin-2-yl, 3-methylisoxazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 3-(pyrrolidine-N-carbonyl)-1,2,4-oxadiazol-5-yl, 3-(*iso*-propylaminocarbonyl)-1,2,4-oxadiazol-5-yl, 5-(ethylaminocarbonyl)-1,2,4-oxadiazol-3-yl, 3-(cyclopropylaminocarbonyl)-1,2,4-oxadiazol-5-yl, 3-(*iso*-propyl(methyl)aminocarbonyl)-1,2,4-oxadiazol-5-yl, 1-*iso*-propyltetrazol-5-yl, tetrazol-5-yl, 2-amino-1,3,4-triazol-5-yl, 5-methylisoxazol-3-yl, 1-methylpyrazol-4-yl, 2-methylaminocarbonyl-1,3,4-oxadiazol-5-yl, 2-ethylaminocarbonyl-1,3,4-oxadiazol-5-yl, 2-(*iso*-propylaminocarbonyl)-1,3,4-oxadiazol-5-yl, 2-carboxyfuran-5-yl, 2-(ethoxycarbonyl)furan-5-yl, 2-(methylaminocarbonyl)furan-5-yl, 2-(ethylaminocarbonyl)furan-5-yl, 2-(*iso*-propylaminocarbonyl)furan-5-yl, 1-methylpyrazol-3-yl, pyrazol-3-yl, 3-methylpyrazol-5-yl, 3-(ethoxycarbonyl)isoxazol-5-yl, 2-methyltetrazol-5-yl, 3-(methylaminocarbonyl)furan-5-yl, 3-(ethylaminocarbonyl)furan-5-yl, 3-(*iso*-propylaminocarbonyl)furan-5-yl, 3-(methylaminocarbonyl)isoxazol-5-yl, 3-(ethylaminocarbonyl)isoxazol-5-yl, 3-(dimethylaminocarbonyl)isoxazol-5-yl, 3-(*iso*-propylaminocarbonyl)isoxazol-5-yl, 4-(methylaminocarbonyl)thiazol-2-yl, 4-(ethylaminocarbonyl)thiazol-2-yl, 4-(dimethylaminocarbonyl)thiazol-2-yl, 4-(*iso*-propylaminocarbonyl)thiazol-2-yl, 4-(ethoxycarbonyl)thiazol-2-yl, 4-carboxythiazol-2-yl, 2-(methylaminocarbonyl)thiophen-5-yl, 2-(ethylaminocarbonyl)thiophen-5-yl, 2-(*iso*-propylaminocarbonyl)thiophen-5-yl, 2-(methylaminocarbonyl)thiophen-4-yl, 2-(ethylaminocarbonyl)thiophen-4-yl, 2-(*iso*-propylaminocarbonyl)thiophen-4-yl, 2-(methoxycarbonyl)thiophen-4-yl, 2-carboxythiophen-4-yl, 2-(methoxycarbonyl)thiophen-5-yl, 2-carboxythiophen-5-yl, 3-(ethoxycarbonyl)furan-5-yl, or 3-carboxyfuran-5-yl.

Suitably, $R^{2'}$ is phenyl substituted with chloro or fluoro or thiophen substituted with chloro.

Preferably, $R^{2'}$ is 2-chlorothiophen-5-yl, 3,4-dichlorophenyl, 3,4-difluorophenyl, 3-chlorophenyl, 4-fluorophenyl, or 3-chloro-4-fluorophenyl.

Suitably, the stereochemistry at the position marked '*' is (S).

Accordingly, there is provided a compound of formula (I') or a salt or solvate thereof.

Suitable salts of the compounds of formula (I) include physiologically acceptable salts and salts which may not be physiologically acceptable but may be useful in the preparation of compounds of formula (I) and physiologically

acceptable salts thereof. If appropriate, acid addition salts may be derived from inorganic or organic acids, for example hydrochlorides, hydrobromides, sulphates, phosphates, acetates, benzoates, citrates, succinates, lactates, tartrates, fumarates, maleates, 1-hydroxy-2-naphthoates, palmoates, methanesulphonates, formates or trifluoroacetates.

Examples of solvates include hydrates.

Certain of the compounds of formula (I) may contain chiral atoms and/or multiple bonds, and hence may exist in one or more stereoisomeric forms. The present invention encompasses all of the stereoisomers of the compounds of formula (I), including geometric isomers and optical isomers, whether as individual stereoisomers or as mixtures thereof including racemic modifications.

Generally it is preferred that a compound of formula (I) is in the form of a single enantiomer or diastereoisomer.

Certain of the compounds of formula (I) may exist in one of several tautomeric forms. It will be understood that the present invention encompasses all of the tautomers of the compounds of formula (I) whether as individual tautomers or as mixtures thereof.

References to 'aryl' refer to monocyclic and bicyclic carbocyclic aromatic rings, for example naphthyl and phenyl, especially phenyl.

Suitable substituents for any aryl group include 1 to 5, suitably 1 to 3, substituents selected from the list consisting of cyano, perhaloalkyl, amido, halo, alkyl, alkoxycarbonyl, mono- and di-(alkyl)aminocarbonyl, alkoxy, nitro, alkylsulphonyl, hydroxy, alkoxyalkyl, alkylthio, mono- and-di-(alkyl)amino, and alkylcarbonylamino.

References to 'heteroaryl' refer to monocyclic heterocyclic aromatic rings containing 1-4 heteroatoms selected from nitrogen, oxygen and sulphur. Examples of heterocyclic aromatic rings include thiophenyl, furanyl, thiazolyl, pyrazinyl, tetrazolyl, triazolyl, oxadiazolyl, oxazolyl, isoxazolyl, and pyrazolyl.

Suitable substituents for any heteroaryl group include 1 to 5, suitably 1 to 3, substituents selected from the list consisting of aminocarbonyl; mono-and di-(alkyl)aminocarbonyl; cycloalkylaminocarbonyl; amino; alkylsulphonylamino; alkylcarbonyl; alkyl; alkoxycarbonyl; unsubstituted heteroaryl; heteroaryl substituted with alkyl, halo, alkoxy, or hydroxy; halo; alkoxy; nitro; alkylsulphonyl; hydroxy; alkoxyalkyl; alkylthio; mono- and-di-(alkyl)amino; alkylcarbonylamino; cyano, perhaloalkyl; amido; and alkylthio.

References to 'alkyl' include references to both straight chain and branched chain aliphatic isomers of the corresponding alkyl, suitably containing up to six carbon atoms.

References to 'cycloalkyl' include saturated alicyclic rings suitably containing 3-8 carbon atoms.

Suitable substituents for any cycloalkyl group include alkyl, halo, and hydroxy.

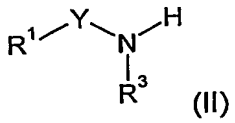
References to 'heterocyclyl' refer to monocyclic heterocyclic aliphatic rings containing 2 to 6, suitably 3 to 5, carbon atoms, and 1 to 3, heteroatoms selected from nitrogen, oxygen, and sulphur. Examples of heterocyclic rings include piperidinyl.

Suitable substituents for any heterocyclyl group include cycloalkylcarbonyl, aminocarbonyl, alkylsulphonylamino, alkylcarbonyl, cycloalkylaminocarbonyl, alkyl, alkoxycarbonyl, alkylaminocarbonyl, halo, alkoxy, nitro, alkylsulphonyl, hydroxy, alkoxyalkyl, alkylthio, mono- and di-(alkyl)amino, and alkylcarbonylamino.

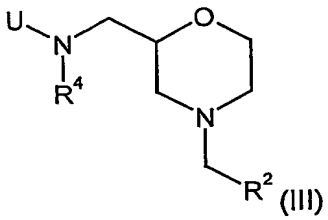
References to 'halogen' or 'halo' refer to iodo, bromo, chloro or fluoro, especially fluoro and chloro.

The compounds of formula (I) and salts and solvates thereof may be prepared by the methodology described hereinafter, constituting a further aspect of this invention.

Accordingly, there is provided a process for the preparation of a compound of formula (I) which process comprises the reaction of a compound of formula (II) with a compound of formula (III);



(II)



(III)

wherein;

R^1, Y, R^3, R^4, and R^2 are as hereinbefore defined for formula (I) and U is a urea-forming group;

and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

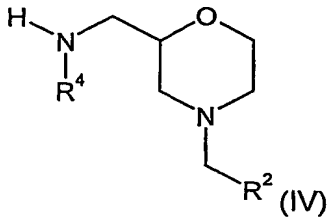
(iii) preparing a salt or solvate of the compound so formed.

A urea-forming group is a group which is derived from a reagent which introduces a carbonyl group and a leaving group to an amino compound. Examples of urea-forming groups are imidazolylcarbonyl and chlorocarbonyl, and, when R^4 is hydrogen, then 4-nitrophenoxycarbonyl may be used. The reagents from which they are derived are 1,1'-carbonyldiimidazole, phosgene,

and 4-nitrophenylchloroformate respectively. A suitable urea-forming group is 4-nitrophenoxycarbonyl.

Typically, the compound of formula (II) and the compound of formula (III) in a suitable solvent, such as an organic solvent, e.g. N,N-dimethylformamide are treated with a suitable base, such as a tertiary amine, e.g. N,N-diisopropylethylamine, at ambient temperature, such as 18 - 25°C.

A compound of formula (III) may be prepared by reaction of a compound of formula (IV);



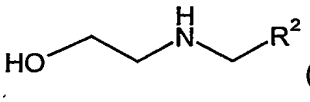
(IV)

wherein R^4 and R^2 are as hereinbefore defined for formula (I);
with a compound of formula U-L wherein U is a urea-forming group as hereinbefore defined and L is a leaving group. A suitable leaving group is a halo group such as chloro.

The reaction between the compound of formula (IV) and the compound U-L is performed in a suitable solvent, for example dichloromethane, in the presence of a suitable base, such as a tertiary amine, for example triethylamine, at a suitable temperature, for example those in the range of -5°C to +5°C over a suitable period of time, for example 3-5 hours.

A compound of formula (IV) wherein R^4 is hydrogen may be prepared either by Reaction (a) or Reaction (c). The S-enantiomer of a compound of formula (IV) may be prepared by Reaction (b).

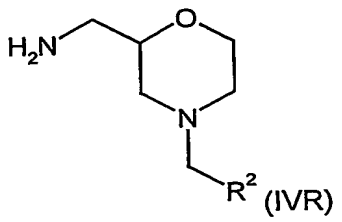
Reaction (a). Reaction of the compound of formula (V) with a compound of formula (VI)



(V)

(VI)

wherein R^2 is as hereinbefore defined for formula (I) and A is a protected amino group, suitably phthalimido, followed by deprotection of the amino group to give a compound of formula (IV) wherein R^4 is hydrogen i.e. a compound of formula (IVR)

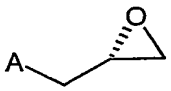


(IVR)

wherein R^2 is as hereinbefore defined, and optionally resolution of the resulting enantiomers of a compound of formula (IVR);

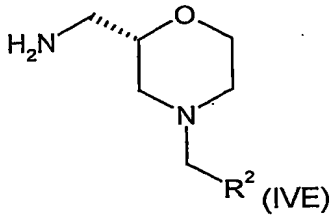
or;

Reaction (b). Reaction of a compound of formula (V) as hereinbefore defined with a compound of formula (VIA)



(VIA)

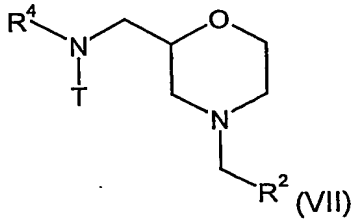
wherein A is as hereinbefore defined for formula (VI), followed by deprotection of the amino group to give the corresponding enantiomer of a compound of formula (IV) wherein R^4 is hydrogen i.e. a compound of formula (IVE)



(IVE)

wherein R^2 is as hereinbefore defined.

Reaction (c). Hydrolysis of a compound of formula (VII);



(VII)

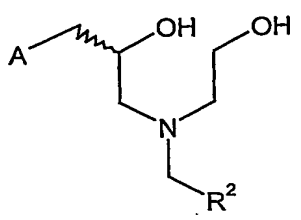
wherein T is trifluoroacetyl, and R^4 and R^2 are as hereinbefore defined for formula (I) and optionally resolution of the resulting enantiomers of a compound of formula (IV).

For both reactions (a) and (b), the cyclisation of the intermediate diols (IVBR) and (IVBE) in the reaction between the compound of formula (V) and a compound of formula (VI) or (VIA) is typically carried out under the Mitsunobu conditions as follows:

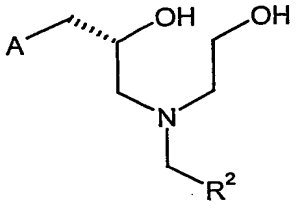
Typically, a mixture of the compound of formula (V) and the compound of formula (VI) or formula (VIA) in a suitable solvent, such as tetrahydrofuran, is stirred, suitably for 20 - 24 hours at a suitable temperature, suitably the reflux temperature of the solvent, under an inert atmosphere, suitably an atmosphere of nitrogen. Further solvent is then added and the mixture cooled, suitably to 0-5°C. A suitable phosphine, such as triphenyl phosphine, is added and the mixture stirred until all the solid is dissolved. A suitable azo compound, such as diisopropylazodicarboxylate, is then added over a period of time, suitably, 10 -15 minutes, while maintaining the temperature at <7°C. The mixture is allowed to stand for a period of time, suitably 2 -3 hours, then allowed to warm, suitably to 20 - 25°C. After a further period of standing, suitably 4-6 hours, further phosphine and azo compounds are added. After a further period of standing, suitably 20-24 hours, the reaction mixture is concentrated to near dryness. A suitable alcohol, suitably propan-2-ol, is added and the concentration step repeated; the alcohol addition and concentration step is then repeated. Further alcohol is then added and the mixture heated to a temperature suitably between 65 - 75°C. After a suitable period, suitably 20 - 45 minutes, the resultant slurry is cooled, suitably to 20 - 25°C, and then allowed to stand, suitably for 1.5 - 3 hours, after which time the product is isolated by filtration. The filter bed is washed with more alcohol and then dried *in vacuo* at 35 - 45°C to yield the protected form of the compound of formula (IVR) or formula (IVE) respectively.

The removal of the protecting group from the product is typically carried out as follows. A slurry of the protected form of the compound of formula (IVR) or formula (IVE) in an appropriate polar solvent, suitably water, is heated to elevated temperature, suitably 70 - 75°C and then treated dropwise with a concentrated mineral acid, suitably concentrated sulphuric acid. The mixture was then heated at elevated temperature, suitably the reflux temperature of the solvent, for a suitable period of time, suitably 20 - 24 hours, after which the reaction mixture was cooled to 20 - 25°C and then treated with a suitable apolar solvent, suitably dichloromethane. A base, suitably 0.880 ammonia solution, is then added dropwise, maintaining the temperature between 20 - 25°C. Further apolar solvent is then added, the aqueous phase then being separated and extracted with further apolar solvent. The combined organic phase is washed with water and then evaporated to dryness. Further apolar solvent is added and re-evaporated to give the compound of formula (IVR) or formula (IVE).

The process for the preparation of the protected form of the compound of formula (IVR) or formula (IVE) described above may also be undertaken in two stages, in which an intermediate compound of formula (IVBR) or of formula (IVBE) respectively;



(IVBR)



(IVBE)

wherein A is as hereinbefore defined for formulae (VI) and (VIA) and R^2 is as hereinbefore defined for formula (I); is isolated.

Typically, a mixture of the compound of formula (V) and a compound of formula (VI) or formula (VIA) in a suitable solvent, such as tetrahydrofuran, is stirred, suitably for 20-24 hours at a suitable temperature, suitably the reflux temperature of the solvent, under an inert atmosphere, suitably an atmosphere of nitrogen. Further compound of formula (V) is added and the mixture heated at a suitable temperature, suitably the reflux temperature of the solvent, under an inert atmosphere, suitably an atmosphere of nitrogen, for a suitable period of time, suitably 3-6 hours. The reaction mixture is then cooled, suitably to 20-25°C, and the compound precipitated by means of addition of a suitable co-solvent, suitably diisopropyl ether. The compound of formula (IVBR) or formula (IVBE) respectively is isolated by filtration, washed with further co-solvent and dried *in vacuo*.

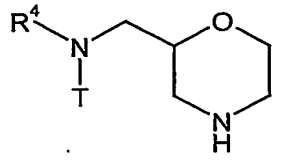
A protected form of the compound of formula (IVR) or formula (IVE) may then be prepared from a compound of formula (IVBR) or formula (IVBE) under similar conditions to those of the reaction between a compound of formula (V) and formulae (VI) or (VIA) as hereinbefore described, but omitting the reflux period prior to the addition of the phosphine and azo compounds.

Reaction (c) is typically carried out by stirring a solution of the compound of formula (VII) in a suitable solvent, for example a mixture of methanol and water, and adding a suitable base, for example potassium carbonate. The mixture is stirred at a suitable temperature, for example those in the range 20 - 25°C for a suitable time, for example 16 - 20 hours followed by removal of the organic solvent in vacuo. Water is then added and the mixture extracted with a suitable organic solvent, for example ethyl acetate. The combined organic phases are washed with water and saturated aqueous sodium chloride solution before drying over a suitable drying agent, for example sodium sulphate, filtering

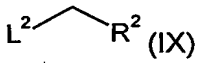
and evaporating the solvent in vacuo. The crude product is then purified by flash chromatography.

The resolution of the compound of formula (IVE) from the racemic product i.e. the compound of formula (IVR) may be undertaken using techniques well known to those skilled in the art, for example preparative chiral high performance liquid chromatography (chiral HPLC) or by fractional crystallisation of diastereoisomeric salts.

A compound of formula (VII) may be prepared by reaction of a compound of formula (VIII) with a compound of formula (IX)



(VIII)



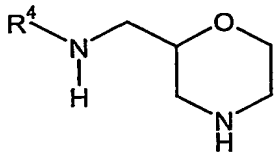
(IX)

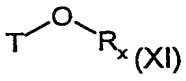
wherein;

T, R^4 and R^2 are as hereinbefore defined for formula (VII) and L^2 is a leaving group. A suitable leaving group, L^2 is a halo group such as chloro.

The reaction between a compound of formula (VIII) and a compound of formula (IX) is typically carried out by stirring a solution of the compound of formula (VIII) in a suitable solvent, for example N,N-dimethylformamide, under an inert atmosphere, for example an atmosphere of nitrogen, with the addition of a suitable base, for example potassium carbonate, and a suitable activating agent, such as sodium iodide. A solution of a compound of formula (IX) in a suitable solvent, such as N,N-dimethylformamide, is added dropwise to the mixture. The mixture is then stirred at a suitable temperature, for example a temperature in the range of 20-25°C, for a suitable period of time, for example 16-20 hours before removing the volatile components in vacuo. The residue is partitioned between a suitable organic solvent, for example dichloromethane, and a saturated aqueous base, for example saturated aqueous sodium carbonate solution. The organic phase is then washed with additional saturated aqueous base and water before drying over a suitable drying agent, for example magnesium sulphate, filtering and evaporation of the solvent in vacuo to yield the crude product. The crude product is purified by flash chromatography.

A compound of formula (VIII) may be prepared by reaction of a compound of formula (X) with a compound of formula (XI);

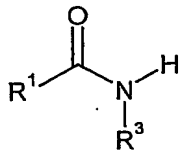

(X)


(XI)

wherein R^4 and T are as hereinbefore defined for formula (VII) and R_x is an alkyl group, suitably ethyl.

The reaction between a compound of formula (X) and a compound of formula (XI) is typically carried out by stirring a solution of a compound of formula (X) in a suitable organic solvent, for example methanol, under an inert atmosphere, for example an atmosphere of nitrogen, and then adding a solution of a compound of formula (XI) in a suitable organic solvent, for example ether. The mixture is then stirred for a suitable period of time, for example 20-40 minutes at a suitable temperature, for example a temperature in the range of 20-25°C and the volatile components removed in vacuo. The residue is then dissolved in a suitable organic solvent, for example methanol, and the volatile components removed in vacuo.

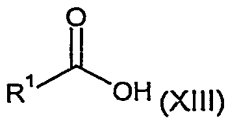
Compounds of formula (II) wherein Y is $-CH_2-$ are either commercially available, or may be prepared by reduction of a compound of formula (XII)


(XII)

wherein R^1 and R^3 are as hereinbefore defined for formula (I), with a suitable reducing agent such as an alkali metal borohydride or diborane-tetrahydrofuran complex.

The reduction of a compound of formula (XII) is typically carried out using lithium borohydride in a suitable organic solvent, such as a mixture of methanol and diglyme, at elevated temperature, conveniently the reflux temperature of the chosen solvent, for a suitable time period, e.g. 1.5 – 3 hours.

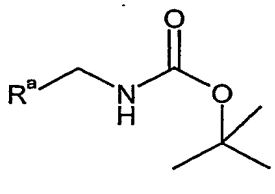
Compounds of formula (XII) are either known, commercially available compounds, or compounds of formula (XII) may be prepared by activation of a compound of formula (XIII) followed by amination thereof;


(XIII)

wherein R^1 is as hereinbefore defined for formula (I). Suitable activating agents are agents which substitute the hydroxy group for a more labile leaving group. A suitable activating agent is thionyl chloride. A suitable amination agent is 0.880 ammonia.

The amination of a compound of formula (XIII) is typically carried out by heating the compound of formula (XIII) together with thionyl chloride at reflux under an inert atmosphere, such as an atmosphere of nitrogen, for a suitable time period, e.g. 1 – 2 hours. Following removal of excess thionyl chloride by evaporation, the residue is dissolved in a suitable solvent, such as a polar organic solvent, e.g. tetrahydrofuran and treated with 0.880 ammonia at ambient temperature, such as about 18 - 25°C.

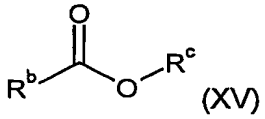
Compounds of formula (II) wherein R^1 is a 1,2,4-oxadiazol-3-yl group substituted at the 5-position, a 1,2,4-oxadiazol-5-yl group substituted at the 3-position, or a 1,3,4-oxadiazol-5-yl substituted at the 2-position, and Y is $-CH_2-$ may be prepared by deprotection of a compound of formula (XIV)

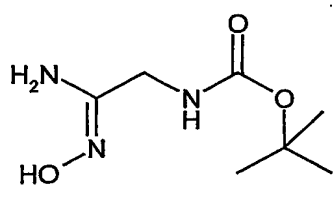

(XIV)

wherein R^a is a 1,2,4-oxadiazol-3-yl group substituted at the 5-position, a 1,2,4-oxadiazol-5-yl group substituted at the 3-position, or a 1,3,4-oxadiazol-5-yl substituted at the 2-position.

Typically, a solution of a compound of formula (XIV) is dissolved in a solution of hydrogen chloride in a suitable solvent, such as 1,4-dioxane and stirred at ambient temperature, such as about 18 - 25°C, for a suitable time period, such as 1 – 2 hours.

A compound of formula (XIV) wherein R^a is 1,2,4-oxadiazol-3-yl may be prepared by reaction of a compound of formula (XV) with the compound of formula (XVI)

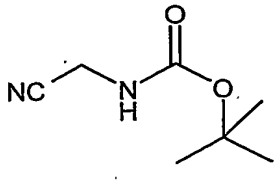

(XV)


(XVI)

wherein R^b is the desired substituent at the 5-position of the 1,2,4-oxadiazol-3-yl moiety and R^c is C_{1-6}alkyl.

Typically, a compound of formula (XV) and the compound of formula (XVI) are dissolved in a suitable solvent, such as an alkanol, e.g. ethanol, and an alkali metal alkoxide, e.g. sodium ethoxide, added. The reaction mixture is heated, conveniently at the reflux temperate of the chosen solvent, over molecular sieves for an appropriate time period, e.g. 2 – 3 hours.

The compound of formula (XVI) may be prepared from the compound of formula (XVII) by reaction with hydroxylamine.



(XVII)

Typically, the reaction between the compound of formula (XVII) and hydroxylamine is carried out in a suitable polar solvent, such as a mixture of an alkanol, e.g. ethanol, and water, in the presence of a suitable base, such as an alkali metal carbonate, e.g. potassium carbonate, at elevated temperature, conveniently the reflux temperature of the chosen solvent, for an appropriate time period, e.g. about 2 days.

The compounds of formulae (V), (VI), (VIII), (IX), (X), (XI), (XII), (XIII), (XV), and (XVII), and certain compounds of formulae (II) and (VII) are known, commercially available compounds and/or may be prepared by analogy with known procedures, for examples those disclosed in standard reference texts of synthetic methodology such as *J. March, Advanced Organic Chemistry, 3rd Edition (1985), Wiley Interscience.*

The compounds of formulae (III), (IVBR), (IVBE) are considered to be novel.

Accordingly, there is provided a compound of formula (III).

There is also therefore provided a compound of formula (IVBR).

There is also therefore provided a compound of formula (IVBE).

The above mentioned conversion of a compound of formula (I) into another compound of formula (I) includes any conversion which may be effected using conventional procedures, but in particular the said conversions include converting one group R^1 into another group R^1.

The above mentioned conversion may be carried out using any appropriate method under conditions determined by the particular groups chosen. Thus, suitable conversions of one group R^1 into another group R^1 include:

(a) converting a group R^1 which represents a heteroaryl group substituted with an alkoxycarbonyl group into a group R^1 which represents a heteroaryl group substituted with a carboxy group; such a conversion may be carried out using an appropriate conventional hydrolysis procedure, for example treating an appropriately protected compound of formula (I) with a suitable aqueous base;

(b) converting a group R^1 which represents a heteroaryl group substituted with a carboxy group into a group R^1 which represents a heteroaryl group substituted with an amide group; such a conversion may be carried out using an appropriate conventional amination procedure, for example treating an appropriately protected compound of formula (I) with a suitable amine in the presence of a suitable peptide coupling agent and, if required, a suitable activating agent;

(c) converting a group R^1 which represents unsubstituted heteroaryl group into a group R^1 which represents an alkylated heteroaryl group; such a conversion may be carried out using an appropriate conventional alkylating procedure, for example treating an appropriately protected compound of formula (I) with an alkyl halide in the presence of a suitable base, and;

(d) converting a group R^1 which represents a heteroaryl group substituted with an alkoxycarbonyl group into a group R^1 which represents a heteroaryl group substituted with an alkylaminocarbonyl, or cycloalkylaminocarbonyl group, or an N-heterocyclylcarbonyl group; such a conversion may be carried out using an appropriate conventional amination procedure, for example treating an appropriately protected compound of formula (I) with an amine.

The above mentioned conversions may as appropriate be carried out on any of the intermediate compounds mentioned herein.

Suitable protecting groups in any of the above mentioned reactions are those used conventionally in the art. The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected, for example those methods discussed in standard reference texts of synthetic methodology such as *P J Kocienski, Protecting Groups, (1994), Thieme.*

For any of the hereinbefore described reactions or processes, conventional methods of heating and cooling may be employed, for example electric heating mantles and ice/salt baths respectively. Conventional methods of purification, for example crystallisation and column chromatography may be used as required.

Where appropriate individual isomeric forms of the compounds of formula (I) may be prepared as individual isomers using conventional procedures such as the fractional crystallisation of diastereoisomeric derivatives or chiral high performance liquid chromatography (chiral HPLC).

The absolute stereochemistry of compounds may be determined using conventional methods, such as X-ray crystallography.

The salts and solvates of the compounds of formula (I) may be prepared and isolated according to conventional procedures.

Compounds of the invention may be tested for *in vitro* biological activity in accordance with the following assays:

(a) CCR-3 Binding Assay

A CCR-3 competition binding SPA (scintillation proximity assay) was used to assess the affinity of novel compounds for CCR-3. Membranes prepared from K562 cells stably expressing CCR-3 (2.5μg/well) were mixed with 0.25mg/well wheat-germ agglutinin SPA beads (Amersham) and incubated in binding buffer (HEPES 50 mM, $CaCl_2$ 1 mM, $MgCl_2$ 5 mM, 0.5% BSA) at 4°C for 1.5 hr. Following incubation, 20 pM of [^{125}I] eotaxin (Amersham) and increasing concentrations of compound (1pM to 30μM) were added and incubated in a 96 well plate for 2 hr at 22°C then counted on a Microbeta plate counter. The total assay volume was 100 μl. Competition binding data were analysed by fitting the data with a four parameter logistic equation. Data are presented as the mean pIC_{50} values (negative logarithm of the concentration of compound which inhibits [^{125}I]eotaxin binding by 50%) from at least two experiments.

(b) Eosinophil Chemotaxis Assay.

Compounds were evaluated for their inhibitory effect on eosinophil chemotaxis. Eosinophils were purified from human peripheral blood by standard CD16 cell depletion using a Miltenyi cell separation column and a magnetic Super Macs magnet as previously described (Motegi & Kita, 1998; J. Immunology. 161:4340-6). Cells were re-suspended in RPMI 1640/10% FCS solution and incubated with calcein-AM (Molecular Probes) at 37°C for 30 mins. Following incubation, the eosinophils were centrifuged at 400g for 5 min and re-suspended in RPMI/FCS at 2.2 million/ml. Cells were then incubated in the presence of increasing concentration of compounds (1 pM to 30 μM) at 37°C for 30 mins. For control responses cells were incubated with RPMI/FCS only. The agonist eotaxin (an EC_{80} concentration) was added to the lower chamber of a 96 well chemotaxis plate (5 μm filter: Receptor Technologies). Eosinophils (50 μl of 2 million/ml cells) were added to the top chamber of the filter plate and incubated at 37°C for 45 mins. Cells remaining on top of the chemotaxis filter were removed and the number of eosinophils which had migrated were quantified by reading the plate on a fluorescent plate reader. Inhibition curves for the effect of compounds on eosinophil chemotaxis were analysed by fitting the data with a four parameter logistic equation. Functional pK_i values (fpK_i) were generated

using the equation below (Lazareno & Birdsall, 1995. Br.J.Pharmacol 109: 1110-9).

$$fpKi = \frac{IC_{50}}{1 + \frac{[Agonist]}{EC_{50}}}$$

The compounds of the Examples were tested in the CCR-3 binding and/or eosinophil chemotaxis assays (assays (a) and (b)). The compounds of the Examples tested in the CCR-3 binding assay possessed pIC50 values in the range 5.0-8.7 The compounds of the Examples tested in the CCR-3 eosinophil chemotaxis assay possessed fpKi values such as those given in the table below:

Example No.	fpKi
8	8.75
11	9.0
19	7.55

Examples of disease states in which the compounds of the invention have potentially beneficial anti-inflammatory effects include diseases of the respiratory tract such as bronchitis (including chronic bronchitis), bronchiectasis, asthma (including allergen-induced asthmatic reactions), chronic obstructive pulmonary disease (COPD), cystic fibrosis, sinusitis and rhinitis.

Also included are diseases of the gastrointestinal tract such as intestinal inflammatory diseases including inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis) and intestinal inflammatory diseases secondary to radiation exposure or allergen exposure.

Furthermore, compounds of the invention may be used to treat nephritis; skin diseases such as psoriasis, eczema, allergic dermatitis and hypersensitivity reactions; and diseases of the central nervous system which have an inflammatory component (eg. Alzheimer's disease, meningitis, multiple sclerosis), HIV and AIDS dementia.

Compounds of the present invention may also be of use in the treatment of nasal polyposis, conjunctivitis or pruritis.

Further examples of disease states in which compounds of the invention have potentially beneficial effects include cardiovascular conditions such as atherosclerosis, peripheral vascular disease and idiopathic hypereosinophilic syndrome.

Compounds of the invention may be useful as immunosuppressive agents and so have use in the treatment of auto-immune diseases such as allograft tissue rejection after transplantation, rheumatoid arthritis and diabetes.

Compounds of the invention may also be useful in inhibiting metastasis.

Diseases of principal interest include asthma, COPD and inflammatory diseases of the upper respiratory tract involving seasonal and perennial rhinitis.

It will be appreciated by those skilled in the art that references herein to treatment or therapy extend to prophylaxis as well as the treatment of established conditions.

As mentioned above, compounds of formula (I) are useful as therapeutic agents.

There is thus provided as a further aspect of the invention a compound of formula (I) or a physiologically acceptable salt or solvate thereof for use as an active therapeutic agent.

There is also therefore provided a compound of formula (I), or a physiologically acceptable salt or solvate thereof, for use in the treatment of inflammatory conditions, e.g. asthma or rhinitis.

According to another aspect of the invention, there is provided the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of inflammatory conditions, eg. asthma or rhinitis.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject suffering from or susceptible to an inflammatory condition e.g. asthma or rhinitis, which method comprises administering an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

The compounds according to the invention may be formulated for administration in any convenient way.

There is thus further provided a pharmaceutical composition comprising a compound of formula (I), or a physiologically acceptable salt or solvate thereof, and optionally one or more physiologically acceptable diluents or carriers.

There is also provided a process for preparing such a pharmaceutical formulation which comprises admixing the compound of formula (I) or a physiologically acceptable salt or solvate thereof with one or more physiologically acceptable diluents or carriers.

The compounds according to the invention may, for example, be formulated for oral, inhaled, intranasal, buccal, parenteral or rectal administration, preferably for oral administration.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol,

tragacanth, mucilage of starch, cellulose or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize- starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl or propyl p- hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds according to the invention may also be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form, for instance as ampoules, vials, small volume infusions or pre-filled syringes, or in multidose containers with an added preservative. The compositions may take such forms as solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory agents such as anti-oxidants, buffers, antimicrobial agents and/or tonicity adjusting agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically into individual sterile containers or by filling a sterile solution aseptically into each container and freeze-drying.

The compounds and pharmaceutical compositions according to the invention may also be used in combination with other therapeutic agents, for example antihistaminic agents, anticholinergic agents, anti-inflammatory agents such as corticosteroids, e.g. fluticasone propionate, beclomethasone dipropionate, mometasone furoate, triamcinolone acetonide or budesonide; or

non-steroidal anti-inflammatory drugs (NSAIDs) eg. sodium cromoglycate, nedocromil sodium, PDE-4 inhibitors, leukotriene antagonists, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists; or beta adrenergic agents such as salmeterol, salbutamol, formoterol, fenoterol or terbutaline and salts thereof; or antiinfective agents e.g. antibiotic agents and antiviral agents. It will be appreciated that when the compounds of the present invention are administered in combination with other therapeutic agents normally administered by the inhaled or intranasal route, that the resultant pharmaceutical composition may be administered by the inhaled or intranasal route.

Compounds of the invention may conveniently be administered in amounts of, for example, 0.001 to 500mg/kg body weight, preferably 0.01 to 500mg/kg body weight, more preferably 0.01 to 100mg/kg body weight, and at any appropriate frequency e.g. 1 to 4 times daily. The precise dosing regimen will of course depend on factors such as the therapeutic indication, the age and condition of the patient, and the particular route of administration chosen.

Throughout the description and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

The invention is illustrated by reference to, but is in no way limited by, the following Examples.

For the avoidance of doubt, the free bond on the R^1 groups as presented in the Tables signifies the point of attachment of the R^1 groups to the residue of the molecule.

It should be noted that, for clarity, compounds of the Descriptions and the Examples are referred to by number, for example "Description 3" and "Example 26". The structures of the compounds so referred to are given in Table 1 for the Examples and Tables 2 to 3 for the Descriptions.

General experimental details

Mass Directed Automated Preparative HPLC column, conditions and eluent

Mass directed automated preparative high performance liquid chromatography was carried out using an LCABZ+ 5µm (5cm x 10mm internal diameter) column, employing gradient elution using two solvent systems, (A) 0.1% formic acid in water, and (B) 95% acetonitrile and 0.5% formic acid in water, at a flow rate of 8ml min^{-1}. Mass spectrometry was carried out using a VG Platform Mass Spectrometer, with an HP1100 Diode Array Detector and Accurate Flow Splitter.

LC/MS System

The following Liquid Chromatography Mass Spectroscopy (LC/MS) System was used:

This system used an 3μm ABZ+PLUS (3.3cm x 4.6mm internal diameter) column, eluting with solvents: A – 0.1%v/v formic acid + 0.077% w/v ammonium acetate in water; and B – 95:5 acetonitrile:water + 0.05%v/v formic acid, at a flow rate of 3 ml per minute. The following gradient protocol was used: 100% A for 0.7mins; A+B mixtures, gradient profile 0 – 100% B over 3.5mins; hold at 100%B for 1.1mins; return to 100% A over 0.2mins.

The LC/MS system used a micromass spectrometer, with electrospray ionisation mode, positive and negative ion switching, mass range 80-1000 a.m.u.

Thermospray Mass Spectra

Thermospray Mass Spectra were determined on a HP 5989A engine mass spectrometer, +ve thermospray, source temperature 250°C, probe temperatures 120°C (stem), 190°C (tip), detection mass range 100-850 a.m.u. Compounds were injected in 10μl of a mixture of solvents comprising 65% methanol and 35% 0.05M aqueous ammonium acetate, at a flow rate of 0.7ml/min.

Solid phase extraction (ion exchange)

'SCX' refers to Isolute Flash SCX-2 sulphonic acid solid phase extraction cartridges.

All temperatures are in °C

Descriptions

Description 1: 2,2,2-Trifluoro-N-(morpholin-2-ylmethyl)acetamide

To a stirred solution of morpholin-2-ylmethylamine (3.1g) in methanol (70ml) under nitrogen was added an ethereal solution of ethyl-α,α,α-trifluoroacetate (5ml in 20ml ether) which had been washed with saturated aqueous sodium bicarbonate, water and brine, and dried. The mixture was stirred for 30 min at 22°C before removal of all volatiles in vacuo. The residue was dissolved in methanol (10ml) and the volatiles again removed in vacuo to give the title compound as a white crunchy foam (4.9g).

Thermospray Mass Spectrum *m/z* 213 [MH^+].

Description 2: N-{[4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2,2,2-trifluoroacetamide

To a stirred solution of Description 1 (3.3g) in N,N-dimethylformamide (50ml) under nitrogen was added potassium carbonate (2.46g) and sodium iodide (2.12g). A solution of 3,4-dichlorobenzyl chloride (2ml) in N,N-dimethylformamide (10ml) was added dropwise to the mixture. The mixture was stirred at 22°C for 18h before the volatiles were removed in vacuo. The residue

was partitioned between dichloromethane (100ml) and saturated aqueous sodium carbonate solution (50ml). The organic phase was subsequently washed with additional saturated aqueous sodium carbonate solution (2 x 50ml) and water (50ml) before drying over magnesium sulphate, filtering and evaporation of the solvent in vacuo to give a pale yellow oil. The oil was purified by Biotage flash chromatography on a 90g silica cartridge eluting with 25% ethyl acetate in cyclohexane, to give the title compound as a colourless oil (2.97g).
LC/MS R_t 2.63 min, Mass Spectrum *m/z* 371 [MH^+].

Description 3: [4-(3,4-Dichlorobenzyl)morpholin-2-yl]methylamine
To a stirred solution of Description 2 (2.97g) in methanol (15ml) and water (5ml) was added potassium carbonate (5.53g). The mixture was stirred at 22°C for 18h before the methanol was removed in vacuo. Water (25ml) was added and the mixture extracted with ethyl acetate (3 x 30ml). The combined organic phases were washed with water (5ml) and saturated aqueous sodium chloride solution (10ml) before drying over sodium sulphate, filtering and evaporation of the solvent in vacuo to give a pale yellow oil. The oil was purified by Biotage flash chromatography on a 90g silica cartridge eluting with 75:8:1 dichloromethane/ethanol/0.880 ammonia solution. The required fractions were combined and the solvent evaporated in vacuo to give the title compound as a colourless oil (1.85g).
LC/MS R_t 1.77 min, Mass Spectrum *m/z* 275 [MH^+].

Description 4: [4-(3,4-Dichlorobenzyl)morpholin-2-yl]methylamine (alternative synthesis)
A mixture of 2-[(3,4-dichlorobenzyl)amino]ethanol (Chem Abs No. 40172-06-3, 0.980g) and 2-(oxiran-2-ylmethyl)-1H-isoindole-1,3(2H)-dione (1.10g) was heated at 80°C under nitrogen for 3h. The resulting solid mass was treated with concentrated sulphuric acid (1.5ml) then stirred at 150°C for 24h. The mixture was treated with water (100ml) then washed with ethyl acetate (2x100ml). The dark aqueous phase was basified to ~pH 12 using 5M aqueous sodium hydroxide, then extracted with ethyl acetate (2x100ml). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and concentrated under vacuum to give the title compound as a brown oil (1.02g).
Mass spec. m/z 275 (MH^+).

Description 5: 1-[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methylamine
Description 3 (racemic mixture, 8g) was separated into its single enantiomers by preparative chiral-HPLC. The separation was carried out using a 2" x 22cm Chiralpak AD 20µm column, Merck self pack DAC system, eluting with 95:5:0.1

(v/v) heptane : absolute ethanol: diethylamine (flow rate: 55ml/min over 40min, UV detection 225nm); sample load preparation: 400mg sample in 20ml 3:2 (v/v) absolute ethanol: system eluent.
The title compound (2.49g) was obtained as follows: preparative HPLC retention time 23.0 min.

Description 5 (Alternative procedure)
A slurry of Description 7 (1.00g) in water (8.5ml) was heated to 75° and then treated dropwise with concentrated sulphuric acid (2.5ml). The mixture was then heated at reflux. After 23h the reaction mixture was cooled to 22° and then treated with dichloromethane (6ml). 880 Ammonia solution (7ml) was then added dropwise with cooling. More dichloromethane (10ml) was added. The aqueous phase was separated and extracted with more dichloromethane (10ml). The combined organic phase was washed with water (5ml) and then evaporated to dryness. The residue was redissolved in dichloromethane and the solvent re-evaporated to give the product as an oil (662mg).

Description 6: 1-[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methanamine salt with D-tartaric acid 1:1
Description 3 (0.613g) was dissolved in methanol (12.3ml). D-Tartaric acid (0.335g) was added and the slurry was heated to reflux for 50min. The mixture was allowed to cool to 0-5°C and the precipitate isolated by filtration to give the title compound as a white solid (0.4g).
ee: 76%ee
Chiral analytical HPLC (Chiralpak AD column, 4.6 x 250mm, eluent 50:50:0.1 MeOH: EtOH: Butylamine, flow rate 0.5ml/min, UV detection at 220nm), Rt 8.9min.

Description 7: Preparation of 2-[4-(3,4-Dichloro-benzyl)-morpholin-2-ylmethyl]-isoindole-1,3-dione
A mixture of 2-[(3,4-dichlorobenzyl)amino]ethanol (2.038 g) and (S)-2-(oxiran-2-ylmethyl)-1H-isoindole-1,3(2H)-dione (2.032g) in tetrahydrofuran (3.3ml) was stirred and heated at reflux under nitrogen. After 21.5h more tetrahydrofuran (12.5ml) was added and the mixture was cooled to 3°. Triphenyl phosphine (2.793g) was added and the mixture was stirred until all the solid had dissolved. Diisopropylazodicarboxylate (2.1ml) was then added over 12min maintaining the temperature at <7°. After 2.25h the mixture was allowed to warm to 22°. After 5.3h more triphenylphosphine (121mg) and diisopropylazodicarboxylate (0.09ml) were added. After 22.5h the reaction mixture was concentrated to near dryness. Propan-2-ol (12ml) was added and the concentration repeated, this was

repeated once more. More propan-2-ol (12ml) was added and the mixture was heated to 70°. After 0.5h the slurry was cooled to 22° and then after a further 2h the product was collected by filtration. The bed was washed with propan-2-ol (2x4ml) and then dried *in vacuo* at 40° to give the product, (2.622g).

Description 8: 4-Nitrophenyl [4-(3,4-dichlorobenzyl)morpholin-2-yl]methylcarbamate

Triethylamine (0.09ml) was added to solution of Description 3 (0.150g, 0.545mmol) in dichloromethane (3ml) with stirring at 20°C under nitrogen. The solution was cooled to 0°C and a solution of 4-nitrophenyl chloroformate (0.121g) in dichloromethane (1ml) was added drop-wise. The resultant mixture was stirred for 4h at 0°C. The solution was allowed to warm to 20°C, washed with brine (4ml), dried ($MgSO_4$), and concentrated in vacuo. Purification by Biotage flash chromatography on silica gel, eluting with 35% ethyl acetate in cyclohexane, gave the title compound (0.2g).

LC-MS (System A) Rt 3.1mins. Mass Spectrum *m/z* 441 [MH^+].

Description 9: 4-Nitrophenyl [(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methylcarbamate

Description 9 was prepared in an analogous manner to Description 8 from Description 5 (0.225g) and 4-nitrophenylchloroformate (0.182g) to yield the title compound (0.2g).

LC-MS Rt 3.1mins. Mass Spectrum *m/z* 441 [MH^+].

Description 10: [(2S)-4-(3,4-difluorobenzyl)morpholin-2-yl]methylamine

Description 10 was made in an analogous manner to that of Description 5.

Preparative HPLC retention time 28.3min

Description 11: 4-Nitrophenyl [(2S)-4-(3,4-difluorobenzyl)morpholin-2-yl]methylcarbamate

Description 11 was prepared in an analogous manner to Description 9 from Description 10 and 4-nitrophenylchloroformate.

LC-MS Rt 2.52mins. Mass Spectrum *m/z* 408 [MH^+].

Description 12: [(2S)-4-(3-chlorobenzyl)morpholin-2-yl]methylamine

Description 12 was made in an analogous manner to that of Description 5.

Chiral preparative HPLC retention time 26.1min

Description 13: {(2S)-4-[(5-chlorothien-2-yl)methyl]morpholin-2-yl}methylamine

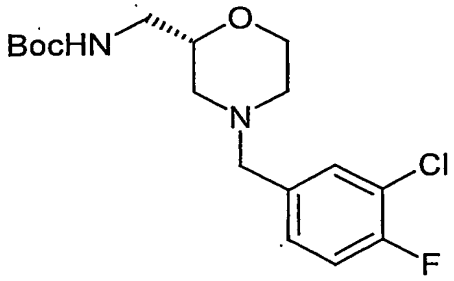
Description 13 was made in an analogous manner to that of Description 5.

Chiral preparative HPLC retention time 25.2min

Description 14: 4-Nitrophenyl [(2S)-4-[(5-chlorothien-2-yl)methyl]morpholin-2-yl]methylcarbamate

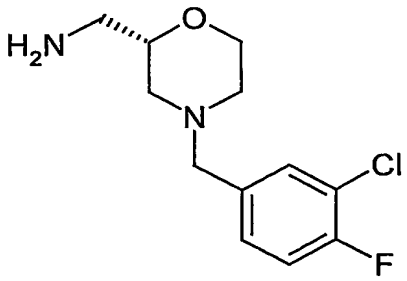
Description 14 was prepared in an analogous manner to Description 9 from Description 13 and 4-nitrophenylchloroformate.
LC-MS Rt 2.58mins. Mass Spectrum *m/z* 412 [MH^+].

Description 16



A solution of (R)-(2-morpholinylmethyl)-carbamic acid 1,1-dimethyl ester [CAS 186202-57-3] (0.26g) in dichloromethane (5ml) was treated with triethylamine (0.167ml) and 3-chloro-4-fluorobenzyl bromide (0.27g). After stirring for 18hrs the mixture was purified by applying directly to an SCX ion exchange cartridge (10g), eluting with methanol followed by 10% 0.880 ammonia/methanol. The basic fraction was evaporated in vacuo to give the title compound (0.37g) as a colourless gum.
LC-MS : Rt = 2.46min. Mass Spectrum *m/z* 359 [MH^+]

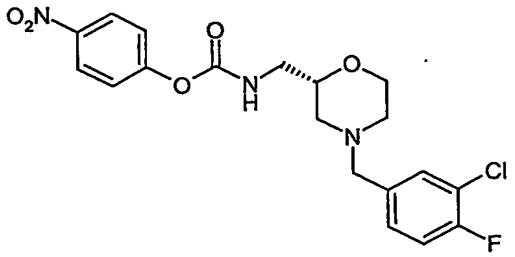
Description 17



A solution of Description 16 (0.36g) in dichloromethane (1ml) was treated with trifluoroacetic acid (1ml) and allowed to stand for 1 hr. The mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane and aqueous sodium bicarbonate; the phases were separated and the organic phase dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to give the title compound (0.25g) as a colourless gum.

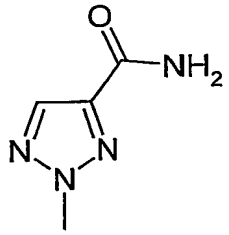
LC-MS : Rt = 0.70min. Mass Spectrum *m/z* 259[MH^+]

Description 18



A solution of 4-nitrophenyl chloroformate (0.102g) in anhydrous dichloromethane (5ml) at 0° was treated, dropwise, with a solution of Description 17 (0.13g) and triethylamine (0.070ml) in anhydrous dichloromethane (2ml). After stirring at room temperature for 18hrs the mixture was concentrated *in vacuo*. Chromatographic purification on silica gel (Varian Bond-Elut cartridge, 5g), eluting with a gradient of ethyl acetate/cyclohexane gave the title compound (0.19g) as a colourless oil.
LC-MS : Rt = 2.66min. Mass Spectrum *m/z* 424 [MH^+]

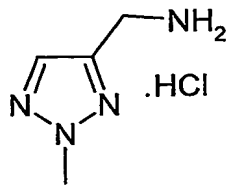
Description 19



2-Methyl- 2H-1,2,3-triazole-4-carboxylic acid (Bull. Soc. Chim. Fr. (1976), (11-12, Pt. 2), 1831-2) (0.127g) was heated under reflux with thionyl chloride (2ml) with stirring under nitrogen for 1.75h. The excess thionyl chloride was evaporated *in vacuo* and the residue dissolved in tetrahydrofuran (8ml). 0.880 ammonia (1ml) was added to the stirred solution at room temperature, and the mixture was stirred at room temperature overnight. The mixture was evaporated to dryness *in vacuo* to give the title compound as a white solid (0.160g).

NMR (D_4-MeOH) δ8.0 (1H,CH); 4.2 (3H,CH_3).

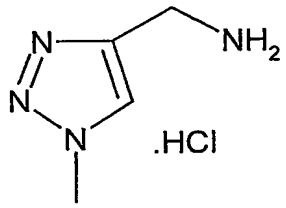
Description 20



A solution of Description 19 (0.160g) in bis(2-methoxyethyl) ether (diglyme, 5ml) was treated with lithium borohydride (0.066g) and heated to reflux (oil bath 155°). Methanol (0.45ml) was added cautiously, and the mixture heated under reflux for 2h with stirring under nitrogen. Saturated aqueous ammonium chloride (0.5ml) was added to the cooled mixture, and the mixture was diluted with methanol (10ml). The solution was applied directly to an Isolute SCX ion exchange cartridge (10g) (pre-eluted with methanol) and eluted with methanol followed by 10% 0.880 ammonia in methanol. The ammonia in methanol fraction was evaporated to low volume (*ca.* 2ml), acidified with 5N aqueous hydrochloric acid (1ml) , and evaporated to dryness *in vacuo* to give the title compound as a white solid (0.026g).

NMR (D_4-MeOH) δ7.7 (1H,CH); 4.2 (3H,CH_3); 4.24, (2H,CH_2).

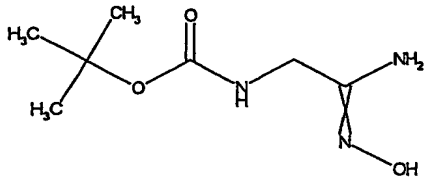
Description 21



A solution of 1-methyl-1H-1,2,3-triazole-4-carboxamide (Bull. Chem. Soc. Jap. (1972), 45(8), 2577-9) (0.050g) in bis(2-methoxyethyl) ether (diglyme, 2ml) was treated with lithium borohydride (0.0264g) and heated to reflux (oil bath 155°). Methanol (0.18ml) was added dropwise in two portions after 5 min and 35 min, and the mixture heated under reflux for 1.5h with stirring under nitrogen. Saturated aqueous ammonium chloride (0.2ml) was added dropwise to the cooled mixture, and the mixture was diluted with methanol (2ml). The solution was applied directly to an Isolute SCX ion exchange cartridge (5g) (pre-eluted with methanol) and eluted with methanol followed by 10% 0.880 ammonia in methanol. The ammonia in methanol fraction was evaporated to low volume (*ca.* 1ml), acidified with 4N hydrogen chloride in 1,4-dioxane (1ml), and evaporated to dryness *in vacuo* to give the title compound (0.030g).

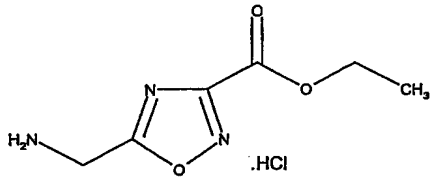
Thermospray Mass Spectrum *m/z* 113 [MH^+]

Description 22



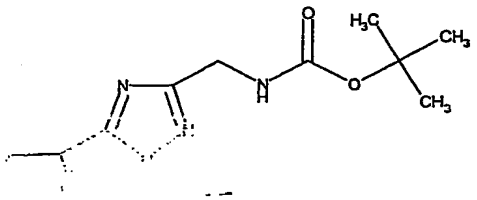
To a solution of N-(tert-butoxycarbonyl)-2-aminoacetonitrile (20.0g) in absolute ethanol (200ml) was added a solution of hydroxylamine (9.0g) and potassium carbonate (17.6g) in water (50ml). The solution was heated to reflux for 2 days. The absolute ethanol was removed *in vacuo* and the aqueous residue extracted with ethyl acetate. The solvent was partially removed *in vacuo* until a precipitate formed. The suspension was cooled and filtered. The residue was washed with ethyl acetate to give the title compound as a white solid (12.84g).
Thermospray Mass Spectrum *m/z* 190 [MH^+].

Description 23



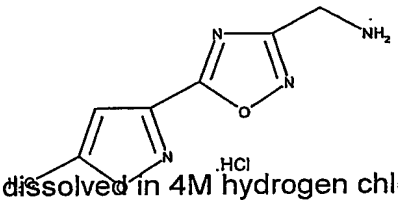
1,2,4-Oxadiazole-3-carboxylic acid, 5-[[[1,1,dimethylethoxy)carbonyl]amino]methyl] ethyl ester (prepared as described in J.Org.Chem (1995),60 (10),3112-20) (0.408g) was dissolved in 4M hydrogen chloride in dioxane (10ml), and the solution stirred at 20° for 0.75h. The solvent was removed *in vacuo* to give the title compound as a light brown solid (0.347g).
^{1}H NMR (D6 DMSO, 400 MHz) δ 1.32 (3H, t, J=7Hz,CH_3), 4.42 (2H, q, J=7Hz,CH_2), 4.58 (2H,s,CH_2) and 9.04 (3H, br s,NH_3^+).

Description 24



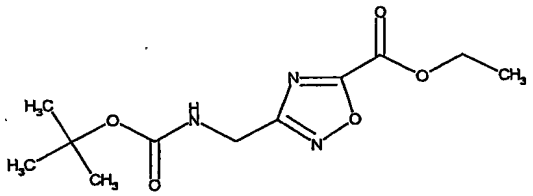
To a solution of Description 22 (0.373g) and ethyl 5-methylisoxazole-3-carboxylate (0.305g) in absolute ethanol (6ml) was added sodium ethoxide (21% wt solution in ethanol, 0.186ml). To the solution was added pre-dried 4A powdered molecular sieves (0.5g). The suspension was heated under reflux for 2.5h. The suspension was filtered and the residue washed with methanol (50ml). The solvent was removed *in vacuo*. The residue was dissolved in dichloromethane (75ml) and the solution was washed with 2N aqueous sodium hydroxide (25ml), 2N hydrochloric acid (25ml), and water (25ml), dried ($MgSO_4$), and concentrated *in vacuo* to give the title compound as a white solid (0.250g). LC/MS R_t 2.7 min *m/z* 298 [MNH_4^+].

Description 25



Description 24 was dissolved in 4M hydrogen chloride in dioxane (3ml), and the solution stirred at 20° for 1.25h. The solvent was removed *in vacuo* to give the title compound as a white solid (0.103g).
Thermospray Mass Spectrum *m/z* 181 [MH^+].

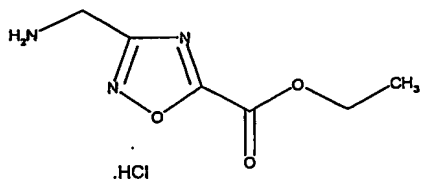
Description 26



To a solution of Description 22 (1.0g) in absolute ethanol (9ml) and sodium ethoxide (21% wt solution in ethanol, 0.5ml) was added diethyl oxalate (2.8ml). Pre-dried 4A powdered molecular sieves (2g) were added, and the suspension was heated under reflux for 3.5h. The suspension was filtered and the residue washed with absolute ethanol (20ml). The solvent was removed *in vacuo*. The residue was dissolved in dichloromethane (75ml) and the solution was washed

with saturated aqueous sodium hydrogen carbonate (25ml), 2N hydrochloric acid (25ml), and water (25ml), dried ($MgSO_4$), and concentrated *in vacuo* to give the title compound as a white solid (0.418g). LC/MS R_t 2.65 min *m/z* 289 [MNH_4^+].

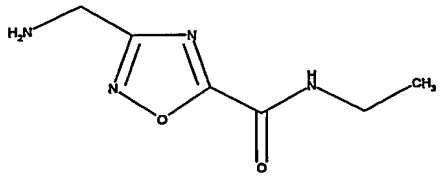
Description 27



Description 26 was dissolved in 4M hydrogen chloride in dioxane (6ml), and the solution stirred at 20° for 1.25h. The solvent was removed *in vacuo* to give the title compound as a colourless gum (0.251g).

^{1}H NMR (D6 DMSO, 400 MHz) δ 1.34 (3H, t, J=6Hz,CH_3), 4.37 (2H, s,CH_2), 4.45 (2H,q, J=6Hz,CH_2) and 8.84 (3H, br s,NH_3^+).

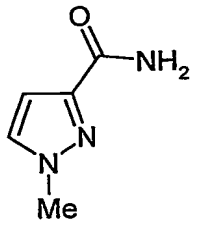
Description 28



To a solution of Description 27 (0.051g) in absolute ethanol (5ml) was added ethylamine hydrochloride (0.2g) and N,N-diisopropylethylamine (0.44ml). The solution was stirred at room temperature for 3h in a sealed vial (Reactivial™). The solution was equally applied onto sulphonic acid ion exchange cartridges (2x10g Isolute SCX, pre-treated with methanol). The cartridges were eluted with methanol followed by 10% 0.880 ammonia in methanol, and the basic fractions were evaporated *in vacuo* to give the title compound (0.037g).

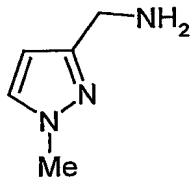
^{1}H NMR (D6 DMSO, 400 MHz) δ 1.10 (3H, t, J=6Hz,CH_3), 3.25 (2H obscured by solvent, q, J=6Hz,CH_2), 3.87 (2H,s,CH_2) and 9.41 (3H, br s,NH_3^+).

Description 29 (1-Methyl-pyrazole-3-carboxamide) [CAS No. 89179-62-4]



A solution of 1-H-pyrazole-3-carboxamide [CAS No:33064-36-7] (0.1g) in tetrahydrofuran (10ml) and N,N-dimethylformamide (5ml) was treated with potassium carbonate (0.12g) and methyl iodide (0.062ml), and the mixture was stirred at room temperature for 3 days. The mixture was diluted with water (50ml) and extracted with ethyl acetate (3x20ml). The aqueous layer was evaporated *in vacuo* and the solid was triturated with ethyl acetate; the extracts were concentrated *in vacuo* to give the title compound (0.08g) as a colourless oil containing *ca.*10% unreacted starting material (1-H-pyrazole-3-carboxamide). LC-MS : Rt = 0.7min. Mass Spectrum *m/z* 126 [MH+].

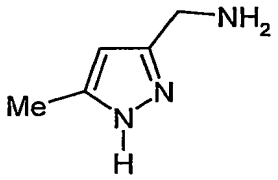
Description 30 (1-Methyl-pyrazole-3-methanamine)



A solution of Description 29 (0.08g) in anhydrous tetrahydrofuran(5ml) was treated with a 1M solution of borane/ tetrahydrofuran complex in tetrahydrofuran (3.5ml) and the mixture was heated at 65° for 18hrs. On cooling the mixture was cautiously quenched by dropwise addition of methanol followed by 2N hydrochloric acid. The solvents were removed by evaporation, and the residue was made basic with triethylamine and concentrated *in vacuo*. The mixture was dissolved in a small volume of methanol applied onto a sulphonic acid SCX ion exchange cartridge (10g), eluting with methanol followed by 10% 0.880 ammonia in methanol. The basic fraction was evaporated *in vacuo* to give the title compound (0.054g) as a colourless oil which also contained ~10% of 1H-pyrazole-3-methanamine [CAS No. 37599-58-9].

1H nmr (D_4MeOH), δ 3.84(2H, s, CH_2); 3.86 (3H, s, Me); 6.28(1H ,m,Ar); 7.53(1H, m, Ar).

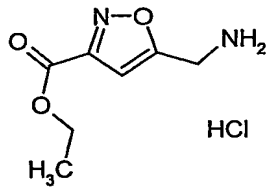
Description 31 (5-Methyl-pyrazole-3-methanamine)



Description 31 was prepared in a similar manner to Description 30 from 5-methyl-pyrazole-3-carboxamide [CAS No. 4027-56-9] (0.09g) to give the title compound(0.035g) as a white solid.

1H nmr (D_4MeOH), δ: 2.08(3H, s, Me); 3.70(2H, s, CH_2); 5.9 (1H, m, Ar).

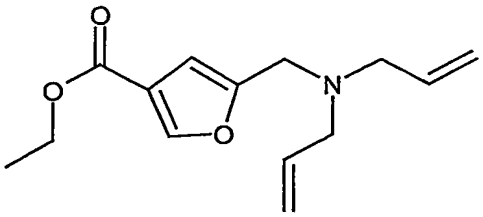
Description 32



To a stirred solution of 5-(tert-butoxycarbonylaminomethyl)-isoxazole-3-carboxylic acid ethyl ester (1.954g) (EP 0451790) in ethanol (15ml) was added a solution of 4.0M hydrogen chloride in 1,4-dioxane (23ml). The mixture was stirred at 20° for 22h and the solvent evaporated *in vacuo* to give the title compound (1.128g) as a pale brown solid.

^{1}H nmr (400MHz, D6 DMSO) 8.86δ (3H, br.s, NH_3^+) 7.05δ (1H, s, *CH*) 4.41-4.33δ (4H, q + br. q, 2xCH_2) 1.32δ (3H, t, CH_3)

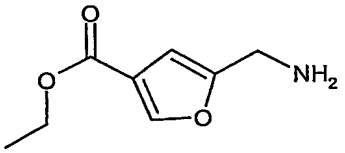
Description 33



To a solution of 5-formyl-3-furancarboxylic acid ethyl ester (prepared as described in Tetrahedron (1996), 52(12), 4245-56) (1.61g) in dichloromethane (20ml) was added diallylamine (1.18ml). The solution was treated with glacial acetic acid (0.55ml) and then sodium triacetoxyborohydride (4.2g). The suspension was stirred at room temperature for 3.5h. The suspension was treated with ethanol (80ml) and stirred at room temperature for 25mins. The solvent was removed *in vacuo*. The residue was partitioned between ethyl

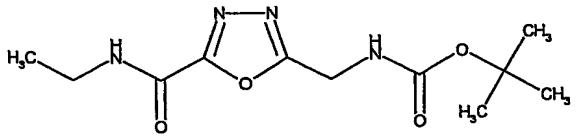
acetate (200ml) and saturated aqueous sodium hydrogen carbonate (100ml). The phases were separated and the organic phase washed with saturated aqueous sodium hydrogen carbonate (100ml) and brine (50ml). The combined aqueous phases were extracted with ethyl acetate (50ml). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was dissolved in methanol and applied equally onto SCX sulphonic acid ion exchange cartridges (10gx4, pre-treated with methanol). The cartridges were eluted with methanol followed by 10% 0.880 ammonia in methanol; evaporation of the basic fractions *in vacuo* gave the title compound as a mobile oil (2.06g). LC/MS R_t 1.76 min *m/z* 250 [MH^+].

Description 34



To a solution of Description 33 in dichloromethane (15ml) was added N,N-dimethylbarbituric acid (4.49g). To the suspension was added palladium tetrakis(triphenylphosphine) (0.130g). The mixture was heated to 35° under nitrogen for 4h. A further amount of palladium tetrakis(triphenylphosphine) (0.150g) was added and the mixture heated for a further 2h. The mixture was applied equally onto SCX sulphonic acid ion exchange cartridges (10gx6, pre-treated with methanol). The cartridges were eluted with methanol followed by 10% 0.880 ammonia in methanol; evaporation of the basic fractions *in vacuo* gave an orange oil. Purification of the residue by Biotage flash chromatography on a 40g silica gel cartridge, eluting with 5% methanol in chloroform gave the title compound a yellow oil (0.573g).
Thermospray Mass Spectrum *m/z* 170 [MH^+]

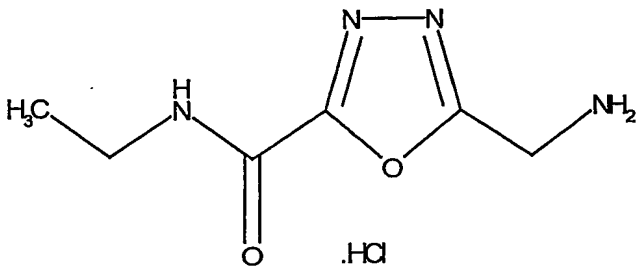
Description 35



To a solution of 5-[[[(1,1-dimethylethoxy)carbonyl]amino]methyl]-1,3,4-oxadiazole-2-carboxylic acid ethyl ester (prepared as described in JOC (1995), 60(10), 3112-20) (0.150g) in methanol (5ml) was added a solution of 2.0M ethylamine in tetrahydrofuran (3ml). The solution was left standing at 20° for

1.5h. The solvent was removed by evaporation using a stream of nitrogen to give the title compound as a yellow gum (0.139g).
LC/MS R_t 2.13 min *m/z* 288 [MNH_4^+].

Description 36

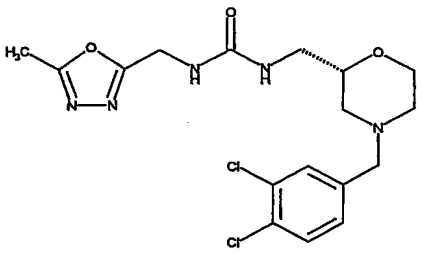


Description 35 (0.133g) was dissolved in 4M hydrogen chloride in dioxane (5ml). The solution was left standing at 20° for 40mins. The solvent was removed by evaporation using a stream of nitrogen to give the title compound (0.113g). Thermospray Mass Spectrum *m/z* 188 [MNH_4^+]

Examples

Synthetic Method A

Example 16

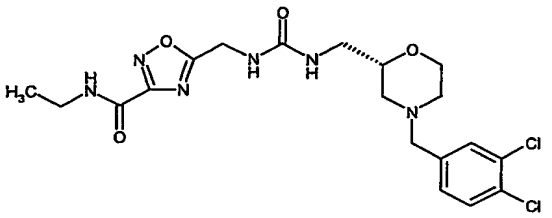


To a solution of 5-methyl-1,3,4-oxadiazole-2-methanamine (prepared as described in Patent DE 3801404) (0.050g) in anhydrous N,N-dimethylformamide (3ml) was added N,N-diisopropylethylamine (0.116ml) and Description 9 (0.147g). The solution was stirred at room temperature for 24h. The solution was applied onto a sulphonic acid ion exchange cartridge (10g Isolute SCX, pre-treated with methanol). The cartridge was eluted with methanol followed by 10% 0.880 ammonia in methanol; evaporation of the basic fraction *in vacuo* gave an oil. Purification of the residue by Biotage flash chromatography on silica gel, eluting with 100:8:1 dichloromethane/ethanol/0.880 ammonia solution, gave a yellow oil. The residue was dissolved in ethyl acetate (50ml) and the solution was

washed with 2N aqueous sodium hydroxide (3x20ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a colourless oil (0.094g).
LC/MS R_t 2.08min m/z 414 [MH^+].

Synthetic Method B (interconversion)

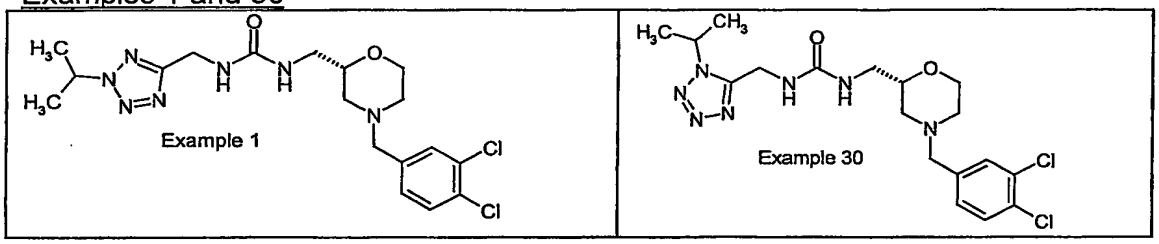
Example 9



To a solution of Example 7 (0.040g) in absolute ethanol (0.7ml) was added ethylamine hydrochloride (0.069g) and then N,N-diisopropylethylamine (0.147ml). The suspension was stirred at room temperature for 18h in a sealed vial. The solvent was removed *in vacuo.* The residue was dissolved in methanol and applied onto a sulphonic acid ion exchange cartridge (5g Isolute SCX, pre-treated with methanol). The cartridge was eluted with methanol followed by 10% 0.880 ammonia in methanol; evaporation of the basic fraction *in vacuo* gave the title compound (0.038g) as a white solid.
LC/MS R_t 2.29 min *m/z* 471 [MH^+].

Synthetic Method C (interconversion)

Examples 1 and 30



To a stirred solution of Example 31 (0.050g) in N,N-dimethylformamide (6ml) was added potassium carbonate (0.040g) followed by 2-iodopropane (0.0138ml). The mixture was stirred at 22° for 18h before being applied to a 2g SCX ion-exchange cartridge (pre-conditioned with methanol). The cartridge was eluted with methanol, followed by 10% 0.880 ammonia solution in methanol. The first ammonia fraction was evaporated *in vacuo* and the residue further purified by Biotage™ flash chromatography on silica gel, eluting with 150:8:1 dichloromethane/ethanol/0.880 ammonia solution. The fractions of the first

eluting product were combined and the solvent evaporated *in vacuo* to give the title compound (Example 1) (0.0307g) as a colourless glass.

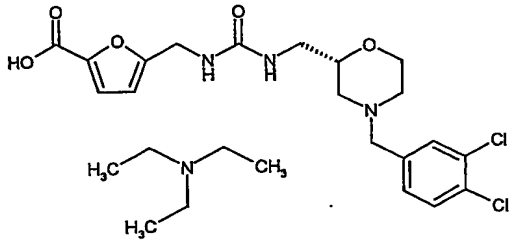
LC/MS : R_t = 2.33min, *m/z* 442,444 [MH^+]

The fractions of the second eluting product were combined and the solvent evaporated *in vacuo* to give the title compound (Example 30) (0.0079g) as a colourless glass.

LC/MS : R_t = 2.31min, *m/z* 442,444 [MH^+]

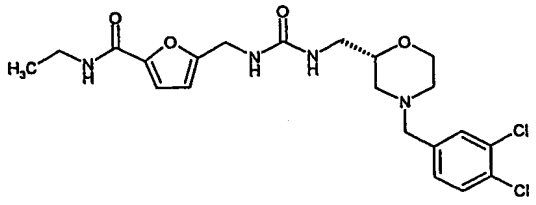
Synthetic Method D

Example 41 (interconversion)



To a solution of Example 42 (0.208g) in methanol (5.5ml) was added 2N sodium hydroxide (1ml). The solution was stirred at 20° for 1.5h. A further amount of 2N sodium hydroxide (1ml) was added and the solution stirred for a further 2h at 20°. The solvent was removed *in vacuo*. The residue was dissolved in water (5ml) and acidified to pH1 using 2N hydrochloric acid. The suspension was applied onto a sulphonic acid ion exchange cartridge (10g Isolute SCX, pre-treated with water). The cartridge was eluted with water followed by 10% triethylamine in methanol; evaporation of the basic fraction *in vacuo* gave the title compound as a colourless glass (0.195g).
LC/MS R_t 2.13min *m/z* 442 [MH^+].

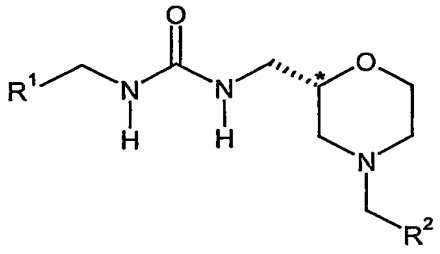
Example 44

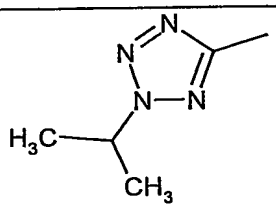
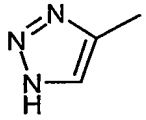
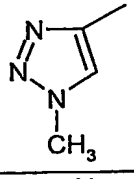
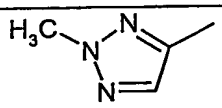
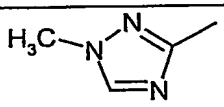
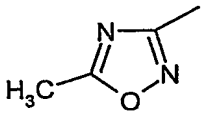


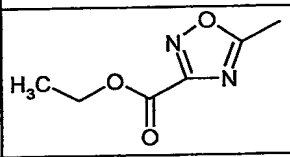
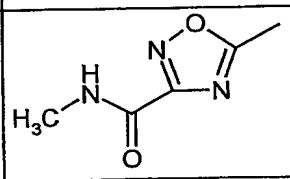
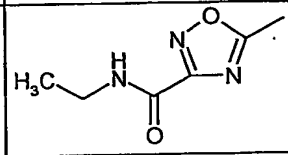
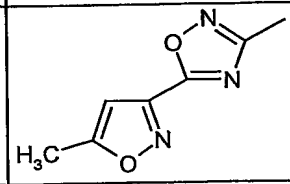
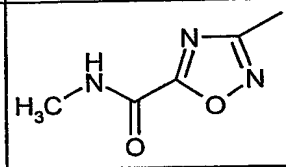
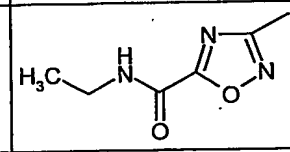
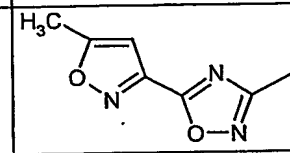
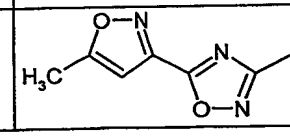
To a solution of Example 41 in N,N-dimethylformamide (2ml) was added 1-hydroxybenzotriazole (0.015g), and ethylamine hydrochloride (0.042g). To the suspension was added N,N-diisopropylethylamine (0.09ml) and then 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.02g). After stirring at room temperature for 16h, further amounts of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.030g), ethylamine hydrochloride (0.02g) and N,N-diisopropylethylamine (0.09ml) were added. The mixture was stirred for a further 3h at room temperature. The mixture was partitioned between ethyl acetate (60ml) and 2N sodium hydroxide (20ml). The phases were separated and the organic phase washed with 2N sodium hydroxide (20ml) and water (20ml), dried ($MgSO_4$), and filtered. The solvent was removed *in vacuo*. The residue was dissolved in methanol and applied onto a sulphonic acid ion exchange cartridge (1g Isolute SCX, pre-treated with methanol). The cartridge was eluted with methanol followed by 10% 0.880 ammonia in methanol. The solvent was removed from the basic fraction by evaporation under a stream of nitrogen. The residue was purified by mass directed preparative HPLC to give the title compound as a colourless gum (0.0064g).
LC/MS R_t 2.15 min *m/z* 469 [MH^+].

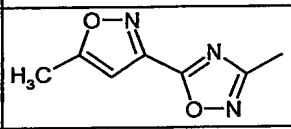
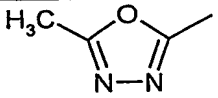
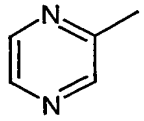
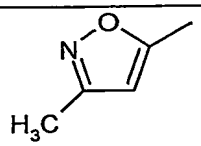
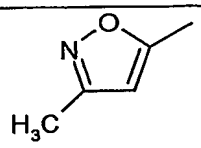
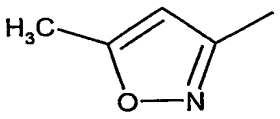
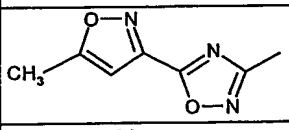
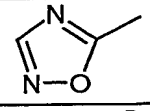
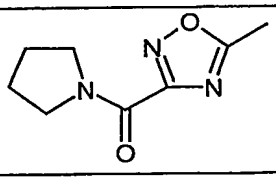
The further examples described in the following Tables were prepared according to or by analogy with the methods hereinbefore described.

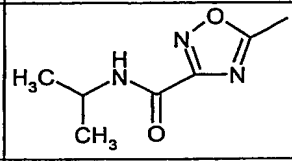
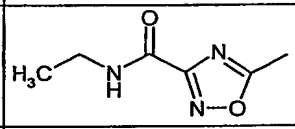
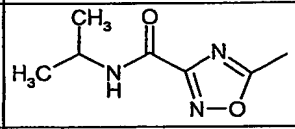
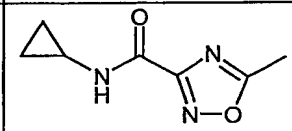
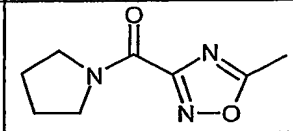
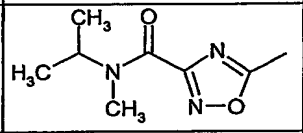
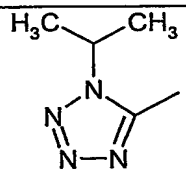
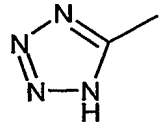
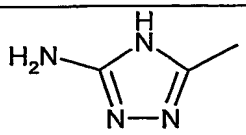
Table 1

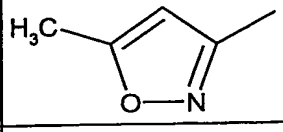
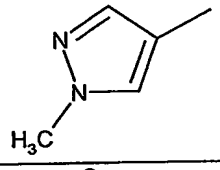
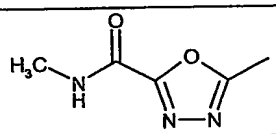
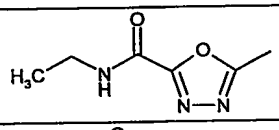
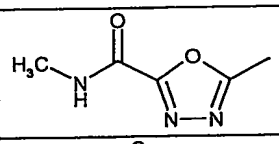
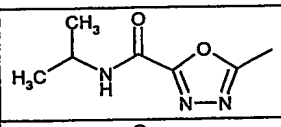
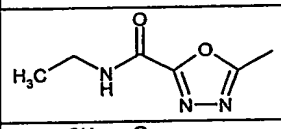
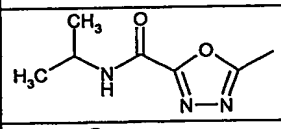
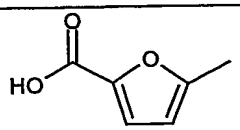
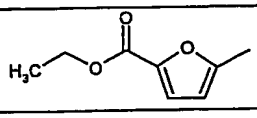


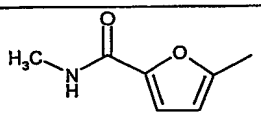
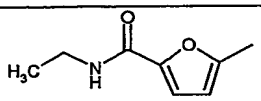
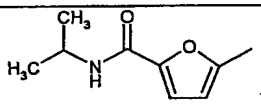
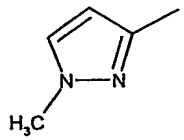
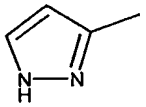
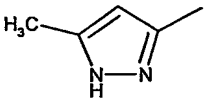
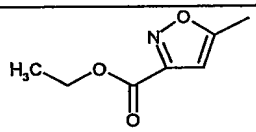
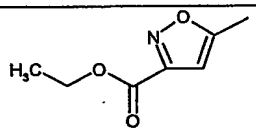
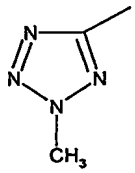
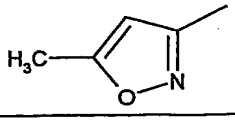
Ex. No.	Synthetic Method	R^1	R^2	Stereochem at position (*)	Calculated Mol. Wt. (as free base)	Observed Mol. Wt. (LC/MS) $[M+H]^+$ of lowest mass isomer unless otherwise indicated
1	C		3,4-di-ClPh	S	442.352	442
2*	A		3,4-di-ClPh	S	399.28	399
3*	A		3,4-di-ClPh	S	413.31	413
4	A		3,4-di-ClPh	S	413.31	413
5	A		3,4-di-ClPh	S	413.31	413
6	A		3,4-di-ClPh	S	414.295	414

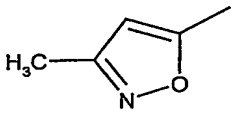
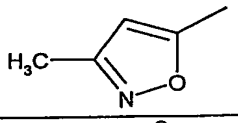
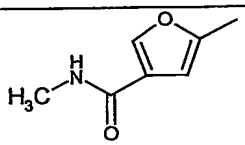
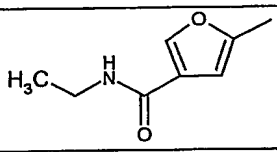
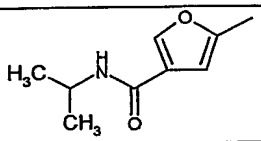
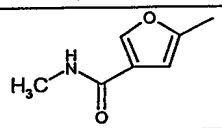
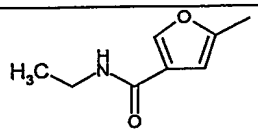
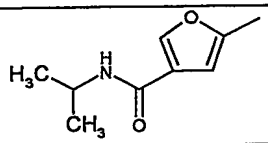
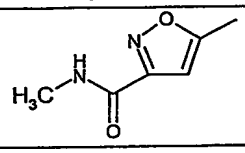
Ex. No.	Synthetic Method	R^1	R^2	Stereochem at position (*)	Calculated Mol. Wt. (as free base)	Observed Mol. Wt. (LC/MS) $[M+H]^+$ of lowest mass isomer unless otherwise indicated
7	A		3,4-di-ClPh	S	472.332	472
8	B		3,4-di-ClPh	S	457.32	457
9	B		3,4-di-ClPh	S	471.347	471
10	A		3,4-di-ClPh	S	481.342	481
11	A		3,4-di-ClPh	S	457.32	457
12	A		3,4-di-ClPh	S	471.347	471
13	A		3,4-di-FPh	S	448.433	449
14	A		3-ClPh	S	446.897	447

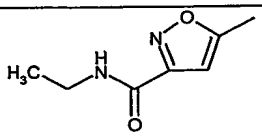
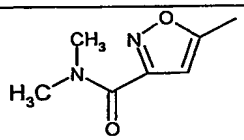
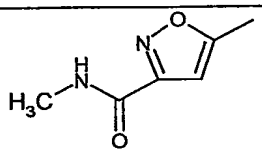
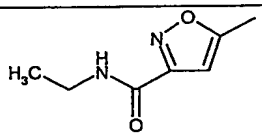
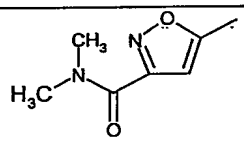
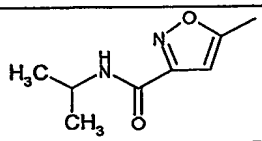
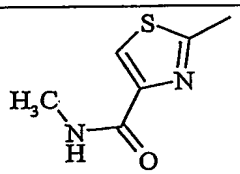
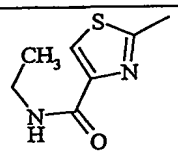
Ex. No.	Synthetic Method	R^1	R^2	Stereochem at position (*)	Calculated Mol. Wt. (as free base)	Observed Mol. Wt. (LC/MS) $[M+H]^+$ of lowest mass isomer unless otherwise indicated
15	A		4-FPh	S	430.442	431
16	A		3,4-di-ClPh	S	414.295	414
17	A		3,4-di-ClPh	S	410.306	410
18	A		3,4-di-ClPh	S	413.307	413
19	A		3,4-di-FPh	S	380.398	381
20	A		3,4-di-ClPh	S	413.31	413
21	A		3-Cl-4-FPh	S	464.888	465
22	A		3,4-di-ClPh	S	400.267	400
23	B		3,4-di-ClPh	S	497.385	497

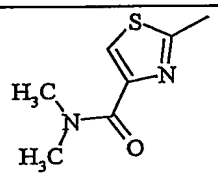
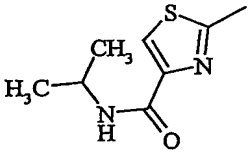
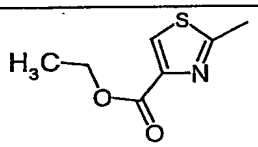
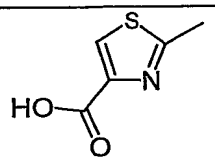
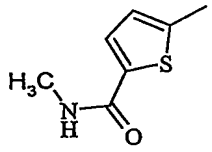
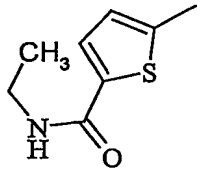
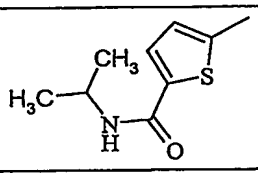
Ex. No.	Synthetic Method	R^1	R^2	Stereochem at position (*)	Calculated Mol. Wt. (as free base)	Observed Mol. Wt. (LC/MS) $[M+H]^+$ of lowest mass isomer unless otherwise indicated
24	B		3,4-di-ClPh	S	485.374	485
25	B		3,4-di-FPh	S	438.438	439
26	B		3,4-di-FPh	S	452.465	453
27	B		3,4-di-FPh	S	450.449	451
28	B		3,4-di-FPh	S	464.476	465
29*	B		3,4-di-FPh	S	466.49	467
30	C		3,4-di-ClPh	S	442.352	442
31	A		3,4-di-ClPh	S	400.27	400
32	A		3,4-di-ClPh	S	414.297	414

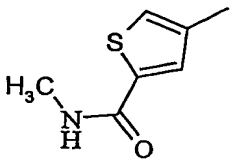
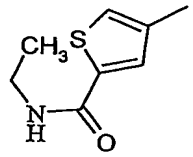
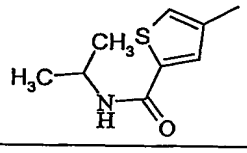
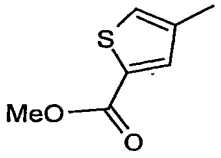
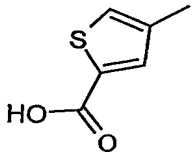
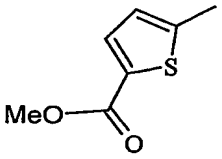
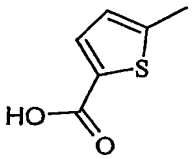
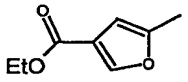
Ex. No.	Synthetic Method	R^1	R^2	Stereochem at position (*)	Calculated Mol. Wt. (as free base)	Observed Mol. Wt. (LC/MS) $[M+H]^+$ of lowest mass isomer unless otherwise indicated
33	A		3,4-di-FPh	S	380.4	381
34	A		3,4-di-ClPh	S	412.32	412
35	A		3,4-di-ClPh	S	457.32	457
36	A		3,4-di-ClPh	S	471.35	471
37	A		3,4-di-FPh	S	424.41	425
38*	A		3,4-di-ClPh	S	485.37	485
39*	A		3,4-di-FPh	S	438.43	439
40*	A		3,4-di-FPh	S	452.46	453
41**	D		3,4-di-ClPh	S	442.30	442
42	A		3,4-di-ClPh	S	470.36	470

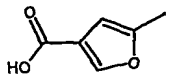
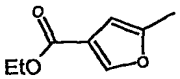
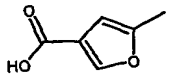
Ex. No.	Synthetic Method	R^1	R^2	Stereochem at position (*)	Calculated Mol. Wt. (as free base)	Observed Mol. Wt. (LC/MS) $[M+H]^+$ of lowest mass isomer unless otherwise indicated
43	D		3,4-di-ClPh	S	455.35	455
44	D		3,4-di-ClPh	S	469.37	469
45	D		3,4-di-ClPh	S	483.4	483
46	A		3,4-di-ClPh	S	412.32	412
47	A		3,4-di-ClPh	S	398.3	398
48	A		3,4-di-ClPh	S	412.32	412
49	A		3,4-di-FPh	S	438.44	439
50	A		3,4-di-ClPh	S	471.34	471
51	A		3-Cl,4-FPh	S	397.84	398
52	A		3-Cl,4-FPh	S	396.85	397

Ex. No.	Synthetic Method	R^1	R^2	Stereochem at position (*)	Calculated Mol. Wt. (as free base)	Observed Mol. Wt. (LC/MS) $[M+H]^+$ of lowest mass isomer unless otherwise indicated
53	A		3-Cl,4-FPh	S	396.85	397
54	A		2-chloro-thiophen-5-yl	S	384.89	385
55	A+D		3,4-di-ClPh	S	455.35	455
56	A+D		3,4-di-ClPh	S	469.37	469
57	A+D		3,4-di-ClPh	S	483.4	483
58	A+D		3,4-di-FPh	S	422.43	423
59	A+D		3,4-di-FPh	S	436.46	437
60	A+D		3,4-di-FPh	S	450.49	451
61	A+B		3,4-di-ClPh	S	456.33	456

Ex. No.	Synthetic Method	R^1	R^2	Stereochem at position (*)	Calculated Mol. Wt. (as free base)	Observed Mol. Wt. (LC/MS) $[M+H]^+$ of lowest mass isomer unless otherwise indicated
62	A+B		3,4-di-ClPh	S	470.36	470
63	A+B		3,4-di-ClPh	S	470.36	470
64	A+B		3,4-di-FPh	S	423.42	424
65	A+B		3,4-di-FPh	S	437.45	438
66	A+B		3,4-di-FPh	S	437.45	438
67	A+B		3,4-di-FPh	S	451.48	452
68	A+D		3,4-di-FPh	S	439.48	440
69	A+D		3,4-di-FPh	S	453.51	454

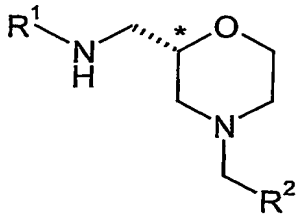
Ex. No.	Synthetic Method	R^1	R^2	Stereochem at position (*)	Calculated Mol. Wt. (as free base)	Observed Mol. Wt. (LC/MS) $[M+H]^+$ of lowest mass isomer unless otherwise indicated
70	A+D		3,4-di-FPh	S	453.51	454
71	A+D		3,4-di-FPh	S	467.54	468
72	A		3,4-di-FPh	S	454.5	455
73	A+D		3,4-di-FPh	S	426.44	427
74	A+D		3,4-di-FPh	S	438.52	439
75	A+D		3,4-di-FPh	S	452.52	453
76	A+D		3,4-di-FPh	S	466.54	467

Ex. No.	Synthetic Method	R^1	R^2	Stereochem at position (*)	Calculated Mol. Wt. (as free base)	Observed Mol. Wt. (LC/MS) $[M+H]^+$ of lowest mass isomer unless otherwise indicated
77	A+D		3,4-di-FPh	S	438.52	439
78	A+D		3,4-di-FPh	S	452.52	453
79	A+D		3,4-di-FPh	S	466.54	467
80	A		3,4-di-FPh	S	439.48	440
81	A+D		3,4-di-FPh	S	425.45	426
82	A		3,4-di-FPh	S	439.48	440
83	A+D		3,4-di-FPh	S	425.45	426
84	A		3,4-di-ClPh	S	470.35	470

Ex. No.	Synthetic Method	R^1	R^2	Stereochem at position (*)	Calculated Mol. Wt. (as free base)	Observed Mol. Wt. (LC/MS) $[M+H]^+$ of lowest mass isomer unless otherwise indicated
85	A+D		3,4-di-ClPh	S	442.3	442
86	A		3,4-di-FPh	S	437.44	438
87	A+D		3,4-di-FPh	S	409.39	410

* Examples 2, 3, 20, and 29 are formate salts
* Examples 38, 39, and 40 are formate salts
** Example 41 is a triethylamine salt

Table 2



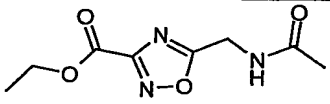
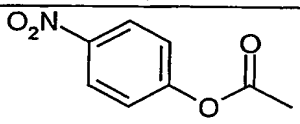
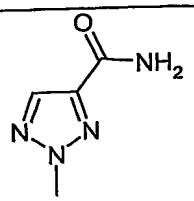
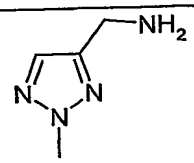
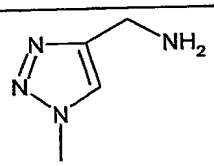
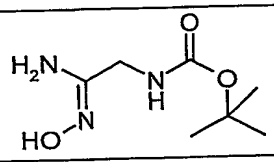
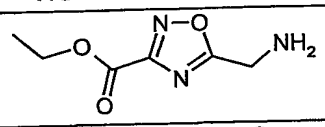
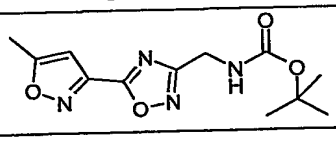
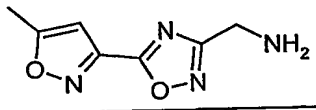
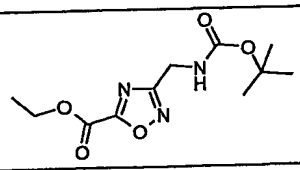
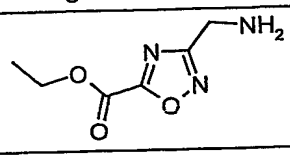
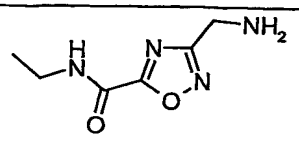
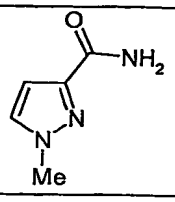
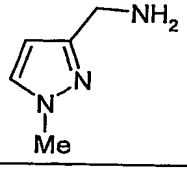
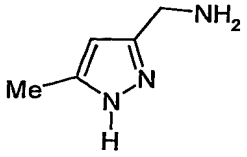
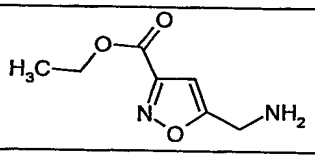
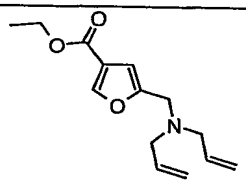
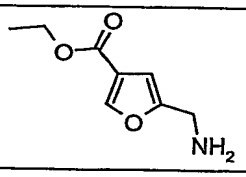
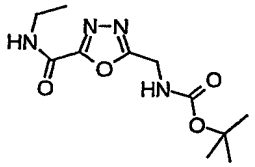
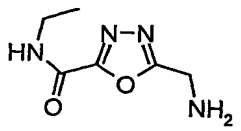
Description No.	R^1	R^2	Stereochem at position (*)
15		3,4-di-ClPh	S
16	tBuOCO	3-Cl,4-F-Ph	S
17	H	3-Cl,4-F-Ph	S
18		3-Cl,4-F-Ph	S

Table 3

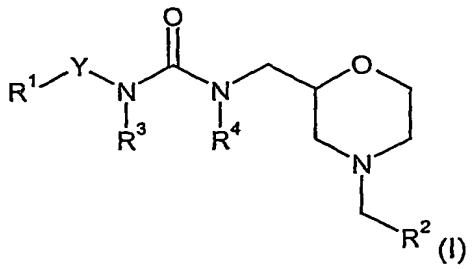
Description No.	Structure
19	
20*	
21*	
22	
23	
24	
25	
26	
27	

28	
29	
30	
31	
32	
33	
34	
35	
36*	

*Descriptions 20, 21, 36 are hydrochloride salts

Claims

1. A compound of formula (I):



wherein:

R^1 represents substituted or unsubstituted heteroaryl;

Y represents $-(CR_{na}R_{nb})_n-$;

R_{na} and R_{nb} are each independently hydrogen or C_{1-6}alkyl;

n is an integer from 1 to 5;

R^2 represents unsubstituted or substituted aryl or unsubstituted or substituted heteroaryl;

R^3 and R^4 each independently represent hydrogen or C_{1-6}alkyl;

and salts and solvates thereof;

with the proviso that the following compounds are excluded;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(pyridin-3-ylmethyl)urea;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[(6-methoxypyridin-3-yl)methyl]urea;

5-({[({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]-amino}methyl)nicotinamide;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(1H-indol-5-ylmethyl)urea;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(1H-indol-4-ylmethyl)urea;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[(5-methylisoxazol-3-yl)methyl]urea;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(thien-2-ylmethyl)urea;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(2-thien-2-ylethyl)urea;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-({5-[(dimethylamino)methyl]-2-furyl}methyl)urea;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[(3-methoxyisothiazol-5-yl)methyl]urea;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[(4-methyl-1,3-thiazol-2-yl)methyl]urea;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(1,3-thiazol-2-ylmethyl)urea;

N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[(2-methyl-1,3-thiazol-4-

-yl)methyl]urea;
methyl 2-({[({[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]-
-amino}-methyl)--4-methyl-1,3-thiazole-5-carboxylate;
N-[(5-amino-1-phenyl-1H-pyrazol-4-yl)methyl]-N'-{[4-(3,4-dichlorobenzyl)-
-morpholin-2-yl]methyl}urea;
N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(1H-pyrrolo[2,3-b]pyridin-3-
-ylmethyl)urea;
N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-({5-[(dimethylamino)-
-methyl]thien-2-yl}methyl)urea;
N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(2-furylmethyl)urea;
N-{[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[(2-methyl-2H-tetraazol-
-5-yl)methyl]urea;
N-{[3-(4-chlorophenyl)isoxazol-5-yl]methyl}-N'-{[(2S)-4-(3,4-dichlorobenzyl)-
-morpholin-2-yl]methyl}urea;
N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[(2-methyl-2H-tetraazol-
-5-yl)methyl]urea;
N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-[(4-methyl-1,3-thiazol-2-
-yl)methyl]urea;
N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-(1,3-thiazol-2-ylmethyl)-
-urea, and;
N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-N'-{[3-(4-methoxyphenyl)-
-isoxazol-5-yl]methyl}urea.

2. A compound of formula (I) according to claim 1 and salts and solvates thereof wherein R^1 is unsubstituted or substituted isoxazolyl, unsubstituted or substituted pyrazinyl, unsubstituted or substituted tetrazolyl, unsubstituted or substituted triazolyl, unsubstituted or substituted pyrazolyl, unsubstituted or substituted furanyl, unsubstituted or substituted thiazolyl, unsubstituted or substituted thiophenyl, or unsubstituted or substituted oxadiazolyl.

3. A compound of formula (I) according to claim 1 or claim 2 and salts and solvates thereof wherein R^1 is 2-(*iso*-propyl)tetrazol-5-yl, 1,2,3-triazol-4-yl, 1-methyl-1,2,3-triazol-4-yl, 2-methyl-1,2,3-triazol-4-yl, 1-methyl-1,2,4-triazol-3-yl, 5-methyl-1,2,4-oxadiazol-3-yl, 3-ethoxycarbonyl-1,2,4-oxadiazol-5-yl, 3-methylaminocarbonyl-1,2,4-oxadiazol-5-yl, 3-ethylaminocarbonyl-1,2,4-oxadiazol-5-yl, 5-(5-methylisoxazol-3-yl)-1,2,4-oxadiazol-3-yl, 5-methylaminocarbonyl-1,2,4-oxadiazol-3-yl, 2-methyl-1,3,4-oxadiazol-5-yl, pyrazin-2-yl, 3-methylisoxazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 3-(pyrrolidine-N-carbonyl)-1,2,4-oxadiazol-5-yl, 3-(*iso*-propylaminocarbonyl)-1,2,4-oxadiazol-5-yl, 5-(ethylaminocarbonyl)-1,2,4-oxadiazol-3-yl, 3-

(cyclopropylaminocarbonyl)-1,2,4-oxadiazol-5-yl, 3-(*iso*-propyl(methyl)aminocarbonyl)-1,2,4-oxadiazol-5-yl, 1-*iso*-propyltetrazol-5-yl, tetrazol-5-yl, 2-amino-1,3,4-triazol-5-yl, 5-methylisoxazol-3-yl, 1-methylpyrazol-4-yl, 2-methylaminocarbonyl-1,3,4-oxadiazol-5-yl, 2-ethylaminocarbonyl-1,3,4-oxadiazol-5-yl, 2-(*iso*-propylaminocarbonyl)-1,3,4-oxadiazol-5-yl, 2-carboxyfuran-5-yl, 2-(ethoxycarbonyl)furan-5-yl, 2-(methylaminocarbonyl)furan-5-yl, 2-(ethylaminocarbonyl)furan-5-yl, 2-(*iso*-propylaminocarbonyl)furan-5-yl, 1-methylpyrazol-3-yl, pyrazol-3-yl, 3-methylpyrazol-5-yl, 3-(ethoxycarbonyl)isoxazol-5-yl, 2-methyltetrazol-5-yl, 3-(methylaminocarbonyl)furan-5-yl, 3-(ethylaminocarbonyl)furan-5-yl, 3-(*iso*-propylaminocarbonyl)furan-5-yl, 3-(methylaminocarbonyl)isoxazol-5-yl, 3-(ethylaminocarbonyl)isoxazol-5-yl, 3-(dimethylaminocarbonyl)isoxazol-5-yl, 3-(*iso*-propylaminocarbonyl)isoxazol-5-yl, 4-(methylaminocarbonyl)thiazol-2-yl, 4-(ethylaminocarbonyl)thiazol-2-yl, 4-(dimethylaminocarbonyl)thiazol-2-yl, 4-(*iso*-propylaminocarbonyl)thiazol-2-yl, 4-(ethoxycarbonyl)thiazol-2-yl, 4-carboxythiazol-2-yl, 2-(methylaminocarbonyl)thiophen-5-yl, 2-(ethylaminocarbonyl)thiophen-5-yl, 2-(*iso*-propylaminocarbonyl)thiophen-5-yl, 2-(methylaminocarbonyl)thiophen-4-yl, 2-(ethylaminocarbonyl)thiophen-4-yl, 2-(*iso*-propylaminocarbonyl)thiophen-4-yl, 2-(methoxycarbonyl)thiophen-4-yl, 2-carboxythiophen-4-yl, 2-(methoxycarbonyl)thiophen-5-yl, 2-carboxythiophen-5-yl, 3-(ethoxycarbonyl)furan-5-yl, or 3-carboxyfuran-5-yl.

4. A compound of formula (I) according to any one of claims 1 to 3 and salts and solvates thereof wherein R_{na} and R_{nb} are both hydrogen.

5. A compound of formula (I) according to any one of claims 1 to 4 and salts and solvates thereof wherein n is 1.

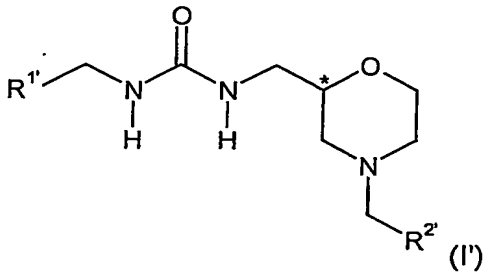
6. A compound of formula (I) according to any one of claims 1 to 5 and salts and solvates thereof wherein R^3 and R^4 are both hydrogen.

7. A compound of formula (I) according to any one of claims 1 to 6 and salts and solvates thereof wherein R^2 is unsubstituted or substituted phenyl or unsubstituted or substituted thiophenyl.

8. A compound of formula (I) according to any one of claims 1 to 7 and salts and solvates thereof wherein R^2 is phenyl substituted with chloro or fluoro.

9. A compound of formula (I) according to any one of claims 1 to 8 and salts and solvates thereof wherein R^2 is 3-chloro-4-fluorophenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl, 3-chlorophenyl, 2-chlorothiophen-5-yl, or 4-fluorophenyl.

10. A compound of formula (I') according to claim 1 and salts and solvates thereof



(I')

wherein;

$R^{1'}$ is unsubstituted or substituted heteroaryl, and;

$R^{2'}$ is phenyl substituted by halo.

11. A compound of formula (I') according to claim 10 and salts and solvates thereof wherein $R^{1'}$ is unsubstituted or substituted furanyl, unsubstituted or substituted pyrazolyl, unsubstituted or substituted tetrazolyl, unsubstituted or substituted triazolyl, unsubstituted or substituted oxadiazolyl, unsubstituted or substituted pyrazinyl, unsubstituted or substituted thiazolyl, unsubstituted or substituted thiophenyl, or unsubstituted or substituted isoxazolyl.

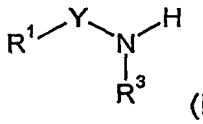
12. A compound of formula (I') according to claim 10 or claim 11 and salts and solvates thereof wherein $R^{1'}$ is 2-(*iso*-propyl)tetrazol-5-yl, 1,2,3-triazol-4-yl, 1-methyl-1,2,3-triazol-4-yl, 2-methyl-1,2,3-triazol-4-yl, 1-methyl-1,2,4-triazol-3-yl, 5-methyl-1,2,4-oxadiazol-3-yl, 3-ethoxycarbonyl-1,2,4-oxadiazol-5-yl, 3-methylaminocarbonyl-1,2,4-oxadiazol-5-yl, 3-ethylaminocarbonyl-1,2,4-oxadiazol-5-yl, 5-(5-methylisoxazol-3-yl)-1,2,4-oxadiazol-3-yl, 5-methylaminocarbonyl-1,2,4-oxadiazol-3-yl, 2-methyl-1,3,4-oxadiazol-5-yl, pyrazin-2-yl, 3-methylisoxazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 3-(pyrrolidine-N-carbonyl)-1,2,4-oxadiazol-5-yl, 3-(*iso*-propylaminocarbonyl)-1,2,4-oxadiazol-5-yl, 5-(ethylaminocarbonyl)-1,2,4-oxadiazol-3-yl, 3-(cyclopropylaminocarbonyl)-1,2,4-oxadiazol-5-yl, 3-(*iso*-propyl(methyl)aminocarbonyl)-1,2,4-oxadiazol-5-yl, 1-*iso*-propyltetrazol-5-yl, tetrazol-5-yl, 2-amino-1,3,4-triazol-5-yl, 5-methylisoxazol-3-yl, 1-methylpyrazol-4-yl, 2-methylaminocarbonyl-1,3,4-oxadiazol-5-yl, 2-ethylaminocarbonyl-1,3,4-

oxadiazol-5-yl, 2-(*iso*-propylaminocarbonyl)-1,3,4-oxadiazol-5-yl, 2-carboxyfuran-5-yl, 2-(ethoxycarbonyl)furan-5-yl, 2-(methylaminocarbonyl)furan-5-yl, 2-(ethylaminocarbonyl)furan-5-yl, 2-(*iso*-propylaminocarbonyl)furan-5-yl, 1-methylpyrazol-3-yl, pyrazol-3-yl, 3-methylpyrazol-5-yl, 3-(ethoxycarbonyl)isoxazol-5-yl, 2-methyltetrazol-5-yl, 3-(methylaminocarbonyl)furan-5-yl, 3-(ethylaminocarbonyl)furan-5-yl, 3-(*iso*-propylaminocarbonyl)furan-5-yl, 3-(methylaminocarbonyl)isoxazol-5-yl, 3-(ethylaminocarbonyl)isoxazol-5-yl, 3-(dimethylaminocarbonyl)isoxazol-5-yl, 3-(*iso*-propylaminocarbonyl)isoxazol-5-yl, 4-(methylaminocarbonyl)thiazol-2-yl, 4-(ethylaminocarbonyl)thiazol-2-yl, 4-(dimethylaminocarbonyl)thiazol-2-yl, 4-(*iso*-propylaminocarbonyl)thiazol-2-yl, 4-(ethoxycarbonyl)thiazol-2-yl, 4-carboxythiazol-2-yl, 2-(methylaminocarbonyl)thiophen-5-yl, 2-(ethylaminocarbonyl)thiophen-5-yl, 2-(*iso*-propylaminocarbonyl)thiophen-5-yl, 2-(methylaminocarbonyl)thiophen-4-yl, 2-(ethylaminocarbonyl)thiophen-4-yl, 2-(*iso*-propylaminocarbonyl)thiophen-4-yl, 2-(methoxycarbonyl)thiophen-4-yl, 2-carboxythiophen-4-yl, 2-(methoxycarbonyl)thiophen-5-yl, 2-carboxythiophen-5-yl, 3-(ethoxycarbonyl)furan-5-yl, or 3-carboxyfuran-5-yl.

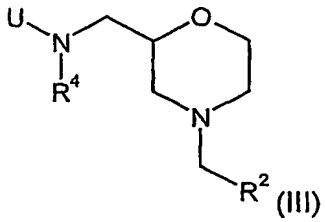
13. A compound of formula (I') according to any one of claims 10 to 12 and salts and solvates thereof wherein $R^{2'}$ is phenyl substituted with chloro or fluoro or thiophen substituted with chloro.

14. A compound of formula (I') according to any one of claims 10 to 13 and salts and solvates thereof wherein $R^{2'}$ is 2-chlorothiophen-5-yl, 3,4-dichlorophenyl, 3,4-difluorophenyl, 3-chlorophenyl, 4-fluorophenyl, or 3-chloro-4-fluorophenyl.

15. A process for the preparation of a compound of formula (I) which process comprises the reaction of a compound of formula (II) with a compound of formula (III);



(II)



(III)

wherein;

R^1, Y, R^3, R^4, and R^2 are as hereinbefore defined for formula (I) in claim 1 and U is a urea-forming group:

and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing a salt or solvate of the compound so formed.

16. A compound of formula (I) as defined in claim 1 or a physiologically acceptable salt or solvate thereof for use as an active therapeutic agent.

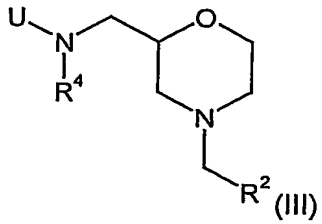
17. A compound of formula (I) as defined in claim 1, or a physiologically acceptable salt or solvate thereof, for use in the treatment of inflammatory conditions, e.g. asthma or rhinitis.

18. Use of a compound of formula (I) as defined in claim 1 or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of inflammatory conditions, eg. asthma or rhinitis.

19. A method for the treatment of a human or animal subject suffering from or susceptible to an inflammatory condition e.g. asthma or rhinitis, which method comprises administering an effective amount of a compound of formula (I) as defined in claim 1 or a physiologically acceptable salt or solvate thereof.

20. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1, or a physiologically acceptable salt or solvate thereof, and optionally one or more physiologically acceptable diluents or carriers.

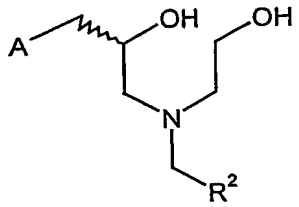
22. A compound of formula (III)



(III)

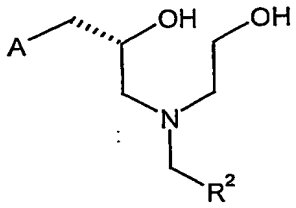
wherein U is a urea forming group, and R^4 and R^2 are as defined for formula (I) in claim 1.

23. A compound of formula (IVBR)



wherein A is a protected amino group and R^2 is as defined for formula (I) in claim 1.

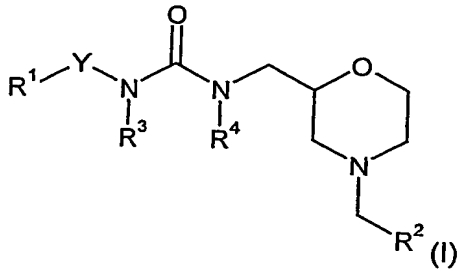
24. A compound of formula (IVBE)



wherein A is a protected amino group and R^2 is as defined for formula (I) in claim 1.

Abstract

Compounds of formula (I):



(I)

wherein:

R^1 represents substituted or unsubstituted heteroaryl;

Y represents $-(CR_{na}R_{nb})_n-$;

R_{na} and R_{nb} are each independently hydrogen or C_{1-6}alkyl;

n is an integer from 1 to 5;

R^2 represents unsubstituted or substituted aryl or unsubstituted or substituted heteroaryl;

R^3 and R^4 each independently represent hydrogen or C_{1-6}alkyl,

and salts and solvates thereof, are CCR-3 antagonists and are thus indicated to be useful in therapy.